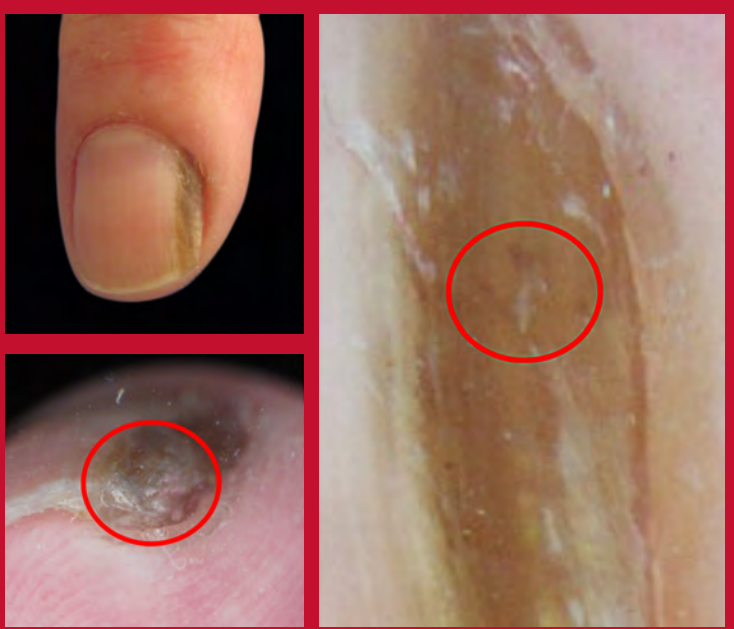
ISSN 1984-5510

Surgical & Cosmetic Dermatology

Volume 11 • Number 1 • January - March 2019

SURGICAL & COSMETIC DERMATOLOGY V.11 N.1 | P.1-80 JAN/MAR 2019

The use of dermatoscopy of the nail plate and its free margin to aid the diganosis of onychomatricoma



Evaluation of the efficacy and safety of microneedling with 5-fluorouracil for the treatment of striae alba: double-blind, randomized clinical trial

Civil responsibility and its consequences for the Dermatology practice

Criobiopsy in dermatological practice

www.surgicalcosmetic.org.br

SOCIEDADE BRASILEIRA DE DERMATOLOGIA

APOIO CIENTÍFICO:

Sociedade Brasileira de Cirurgia Dermatológica

ISSN: 1984-5510
Online ISSN: 1984-8773

Surgical & Cosmetic Dermatology

Publicação Oficial da Sociedade Brasileira de Dermatologia
Publicação Trimestral

www.surgicalcosmetic.org.br

Periodicidade Trimestral

Sociedade Brasileira de Dermatologia
Afiliada à Associação Médica Brasileira
www.sbd.org.br

Surgical & Cosmetic Dermatology

SURGICAL & COSMETIC DERMATOLOGY
Publicação Oficial da Sociedade Brasileira de Dermatologia
Official Publication of Brazilian Society of Dermatology
Publicação Trimestral (Quarterly Edition)
ISSN 1984-5510 ● ISSN-e 1984-8773 ● January - March 2019 ● Volume 11 ● Number 1

Surgical & Cosmetic Dermatology

A/C SURGICAL & COSMETIC DERMATOLOGY

Av. Rio Branco, 39 18º andar
Cep: 20.090-003
Rio de Janeiro-RJ, Brasil.
Fone: 55 (21) 2253-6747
E-mail: surgical@sbd.org.br
website: www.surgicalcosmetic.org.br

A *Surgical & Cosmetic Dermatology* é uma publicação oficial da Sociedade Brasileira de Dermatologia (SBD) em parceria com a Sociedade Brasileira de Cirurgia Dermatológica. O conteúdo técnico-científico apresentado nesta publicação é de co-propriedade da Sociedade Brasileira de Dermatologia.

Editada por: Sociedade Brasileira de Dermatologia.

Informações sobre a Assinatura da Surgical & Cosmetic Dermatology podem ser encontradas no site www.surgicalcosmetic.org.br

A revista consta no Depósito Legal, na Biblioteca Nacional, de acordo com o Decreto nº 1.825, de 20 de dezembro de 1907.

Indexações

- Sumários. org (www.sumarios.org/)
- DOAJ (https://doaj.org/)
- Latindex (www.latindex.org)
- Lilacs (http://bases.bireme.br/)
- SCOPUS (http://www.scopus.com/home.url)
- Periódica (http://periodica.unam.mx)
- Redalyc (http://www.redalyc.org)

PERIODICIDADE TRIMESTRAL

Equipe Técnica
Bruno Abraão de Souza
Marcella Justo
Nazareno Nogueira de Souza

Bibliotecária
Vanessa Zampier

Assinaturas
R$ 250,00 e $180 dólares

Informações de pagamento no site:
www.surgicalcosmetic.org.br

INSTRUÇÕES AOS AUTORES

A Surgical & Cosmetic Dermatology (S&CD), editada em 2009, constitui publicação médica destinada a difundir conhecimento e experiência nas áreas de Cirurgia Dermatológica, Oncologia Cutânea, Estudo de Imagens, Tecnologia em Dermatologia e Dermatologia Cosmética. É uma publicação trimestral da Sociedade Brasileira de Dermatologia (SBD) que conta com o apoio da Sociedade Brasileira de Cirurgia Dermatológica e do Colégio Íbero Latino de Dermatologia, e que baseia sua política ética e editorial nas regras emitidas pelo The International Committee of Medical Journal Editors (www.icmje.org). A revista está disponível na íntegra online e adota a política de acesso aberto. A S&CD não cobra aos autores para que submetam ou publiquem manuscritos, não havendo qualquer tipo de custo ou taxas. A revista adota também a licença de uso da Creative Commons CC BY, https://creativecommons.org/licenses/by/3.0/br/.

Os manuscritos devem estar de acordo com os padrões editoriais para artigos submetidos a periódicos biomédicos estabelecidos na Convenção de Vancouver (Requisitos Uniformes para Manuscritos Submetidos a Revistas Biomédicas), e regras para relatos de ensaios clínicos e revisões sistemáticas (metanálises).

Serão produzidos exemplares impressos da versão em língua portuguesa, com resumos e títulos em inglês. A versão completa em lingua estará disponível nos websites da SBD e da S&CD, no link: www.surgicalcosmetic.org.br.

Nomes de autores e de pareceristas são mantidos em sigilo; a revista adota o sistema de *double blind review.* Todos os artigos propostos à publicação serão previamente submetidos à revisão anônima e confidencial de no mínimo dois membros do Conselho Editorial ou dos Conselhos Nacional e Internacional de Revisores, seguindo as diretrizes do COPE (*Committee on Publication Ethics*).

Quando aceitos, estarão sujeitos a pequenas correções ou modificações que não alterem o estilo do autor.

As pesquisas em seres humanos devem ter a prévia aprovação de um Comitê de Ética em Pesquisa e obedecer aos padrões éticos da Declaração de Helsinki de 1975, revista em 2000, 2008 e 2013.

A S&CD segue o Guia para o registro e publicação de retratação e também o Guia para registro e publicação de errata elaborados pela SciELO, disponível no endereço eletrônico http://www.scielo.org/php/level.php?lang=pt&component=56&item=57

Os autores ao submeterem manuscrito para avaliação da revista devem garantir que o mesmo não contém nenhuma violação de quaisquer direitos autorais ou outro direito de terceiro. A S&CD utiliza software antiplágio para combater o plágio acadêmico e profissional, verificando a originalidade de artigos.

PROCESSO DE AVALIAÇÃO

O processo de avaliação dos artigos submetidos à S&CD ocorre nas seguintes etapas:

- Verificação preliminar: a secretaria editorial verifica a consistência dos dados cadastrais e observância das normas de submissão. Se aprovados os manuscritos são direcionados para a próxima fase, o desk-review.

- ***Desk-review*:** nesta fase o Editor analisa o formato científico do manuscrito quanto aos objetivos, marco teórico, linguagem e metodologia, verificando o enquadramento do artigo ao escopo editorial da revista e o potencial de contribuição da pesquisa. Essa tarefa é dividida entre o editor geral e os editores adjuntos, cada qual em sua área de especialidade. Se aprovados pelos editores os artigos são direcionados para o *double blind review.*

- ***Double blind review*:** o artigo e demais documentos suplementares são encaminhados a pelo menos dois avaliadores, especialistas nacionais ou estrangeiros reconhecidos no assunto dos manuscritos que avaliam, e que não possuam qualquer espécie de vinculação com o trabalho em revisão.

- Após o trabalho receber os pareceres oriundos do estágio double blind review, o editor envia aos autores o resultado pelo sistema de submissão, que poderá referir-se a uma das três situações seguintes:

Aprovação: o artigo foi aceito para publicação e os autores deverão tomar as demais providências cabíveis, mencionadas nestas diretrizes, para que o mesmo seja publicado.

Revisão: os autores deverão realizar as adequações sugeridas, ou apresentarem as devidas argumentações para não procederem. As versões dos autores visando atender as revisões solicitadas pelos pareceristas deverão sempre ser acompanhadas de uma respectiva minuta esclarecendo as alterações atendidas e explicando as razões das não atendidas. O prazo de entrega do artigo revisado é determinado pelo editor e informado aos autores em função da revisão solicitada. Após a entrega do artigo revisado, o mesmo é novamente submetido aos pareceristas para verificação das alterações. A revisão poderá envolver várias rodadas até que se chegue ao parecer final de aprovação ou rejeição do manuscrito.

Rejeição: o artigo não foi aceito para publicação conforme justificativa apresentada pelo editor embasada na avaliação dos pareceristas, que refletem as melhorias a serem realizadas no texto.

- Cabe ao Editor, após o parecer dos avaliadores, revisar e aprovar ou recusar a versão final do trabalho. O editor e editores associados também poderão recusar os manuscritos em avaliação prévia assim que submetidos por não se encaixarem no perfil editorial da revista.

- Durante todo o processo editorial os autores podem acompanhar o status da avaliação, podendo inclusive recorrer de decisões.

*Os casos não previstos nestas diretrizes serão tratados pelo Editor-Chefe da S&CD, e pelo Conselho Editorial quando assim se fizer necessário.

ORIENTAÇÕES PARA O PREPARO DOS ARTIGOS

A preparação correta do manuscrito torna os processos de revisão e publicação mais eficientes. Assim, recomendamos alguns cuidados que podem facilitar significativamente a preparação dos manuscritos.

1. Os artigos devem ser inéditos e redigidos no idioma de origem do autor (português, espanhol ou inglês): a equipe editorial providenciará as versões necessárias. A escolha da fonte deve ser Times New Roman ou Arial, de número 12.
2. O título do trabalho deve ser curto e conciso, informado em português e inglês, com até 150 caracteres sem espaços, acompanhado de um título resumido.
3. Os resumos em português e inglês devem acompanhar o formato adequado ao tipo de artigo.
4. Os autores devem informar o nome com suas abreviaturas, e as suas afiliações institucionais, seguidos de cidade, estado e país. Os vínculos às instituições devem ser citados em ordem hierárquica (ex.1º Departamento, 2º Universidade) e não são permitidas a inclusão dos mini-currículos. Quando um autor é afiliado a mais de uma instituição, cada uma deve ser identificada separadamente. Quando dois ou mais autores estão afiliados à mesma instituição, a sua identificação é feita uma única vez. É obrigatório mencionar o número ORCID, utilizado para a identificação de pesquisadores. O autor deve assumir pelo menos uma responsabilidade na elaboração do trabalho e deverá informar a contribuição de cada um na submissão. Um dos autores deve ser designado como autor correspondente, com endereço de e-mail. Deve também ser citado o local de realização do trabalho.
5. Os autores devem informar claramente se houve conflitos de interesse e suporte financeiro.
6. As palavras-chave devem ser citadas em português e em inglês (Keywords), totalizando 3 a 10 por idioma, devendo ser incluídas em todos os tipos de artigos. É recomendável que estas palavras deverão estar contidas no DeCS (Descritores em Ciências da Saúde) e MeSH (*Medical Subject Headings*) que podem ser acessados na internet.
7. O número limite de palavras para os textos deve ser obedecido segundo o tipo de artigo, e computado excluindo as referências e os resumos em português e inglês.
8. Devem ser evitadas informações introdutórias extensas e repetitivas, dando-se preferência às mais recentes, ainda não publicadas. Evite textos com repetição da mesma informação no resumo, introdução e discussão.
9. Pesos e medidas devem ser expressos no sistema métrico decimal, e temperaturas em graus centígrados.
10. Drogas devem ser mencionadas por seus nomes genéricos, seguidos da dosagem e posologia empregadas, evitando-se a citação de termos comerciais ou marcas. Descrições de quaisquer equipamentos, instrumentos, testes e reagentes devem conter o nome do fabricante e o local de fabricação.
11. De acordo com o ICMJE, apenas podem ser designados como autores, aqueles que participaram ativamente no trabalho, podendo assim assumir a responsabilidade pública pelo seu conteúdo. Os créditos de autoria devem se basear exclusivamente em contribuições substanciais para:
    a- discussão e planejamento do tema e protocolo, análise ou interpretação de dados;
    b- redação do artigo ou sua crítica;
    c- responsabilidade pela aprovação final para a publicação.
    Outras contribuições menores como sugestões de literatura, coleta e análise de dados, obtenção de financiamento, auxílio técnico na execução de rotinas, encaminhamento de pacientes, interpretação de exames de rotina e chefia de serviço ou departamento que não estejam envolvidas no estudo, não constituem critérios para autoria. e podem ser reconhecidas separadamente sob a forma de "agradecimentos", de acordo com a decisão dos autores.
12. As referências bibliográficas devem ser listadas nas últimas páginas do artigo, e numeradas de acordo com a citação no texto (em ordem numérica seqüencial), seguindo o estilo Vancouver, como indicado pelo International Committee of Medical Journal Editors (ICMJE). Referências citadas em legendas de tabelas e figuras devem manter a seqüência com as citações no texto. Todos os autores devem ser citados se forem até seis; acima disso, devem ser mencionados os seis primeiros e "*et al.*". Seguem-se exemplos dos tipos mais comuns de referências. Exemplos de citações no texto retirados do ICMJE:

a-Artigo em periódico:

Hallal AH, Amortegui JD, Jeroukhimov IM, Casillas J, Schulman CI, Manning RJ, *et al*. Magnetic resonance cholangiopancreatography accurately detects common bile duct stones in resolving gallstone pancreatitis. J Am Coll Surg. 2005;200(6):869-75.

b-Capítulo de livro:

Reppert SM. Circadian rhythms: basic aspects and pediatric implications. In: Styne DM, Brook CGD, editors. Current concepts in pediatric endocrinology. New York: Elsevier; 1987. p .91-125.

c-Texto na Internet:

Ex. com autor indicado:

Fugh-Berman A. PharmedOUT [Internet]. Washington: Georgetown University, Department of Physiology and Biophysics; c2006 [cited 2007 Mar 23]. Available from: http://www.pharmedout.org/.

Ex. quando o autor é uma organização:

International Union of Biochemistry and Molecular Biology. Recommendations on Biochemical & Organic Nomenclature, Symbols & Terminology etc. [Internet]. London: University of London, Queen Mary, Department of Chemistry; [updated 2006 Jul 24; cited 2007 Feb 22]. Available from: http://www.chem.qmul.ac.uk/iubmb/.

d- Apresentação prévia em eventos:

Bruhat M, Silva Carvalho JL, Campo R, Fradique A, Dequesne J, Setubal A, editors. Proceedings of the 10th

Congress of the European Society for Gynaecological Endoscopy; 2001 Nov 22-24; Lisbon, Portugal. Bologna (Italy): Monduzzi Editore, International Proceedings Division; c2001. 474 p.

13. Ilustrações (figuras, quadros, gráficos e tabelas) devem ser referidas em ordem numérica sequencial no texto em números arábicos (exemplo: Figura 3, Gráfico 7), cabendo ao Editor suprimir as redundantes. As legendas das figuras e gráficos e os títulos e notas de rodapé das tabelas devem descrever precisamente seu conteúdo com frases curtas, porém suficientes para a compreensão ainda que o artigo não seja totalmente lido. Todos devem ser inseridos no passo correspondente a ilustrações no sistema, evitando que use o campo destinado ao texto para que não contabilizem as palavras dentro das ilustrações.
14. As figuras deverão ter resolução mínima de 300 DPI, largura mínima de 1.200 pixels com altura proporcional, e serem gravadas nos formatos JPG ou TIF. Podem ser colocadas setas ou linhas para localizar as áreas de interesse. As legendas das imagens histológicas devem especificar a coloração e o aumento. Se uma figura já foi publicada anteriormente, deverá citar a fonte original abaixo da mesma e constar nas referências. Deverão enviar à revista a permissão do detentor dos direitos autorais para a sua reprodução. No uso de figuras que identifiquem a face de pacientes será preciso autorização por escrito para divulgação (ver no site da revista o documento Autorização para uso de fotografias).
15. Quanto aos vídeos é necessário inserir legendas contendo informações como título do manuscrito, autoria, instituição e outros comentários pertinentes. No uso de imagens de pacientes, a identidade deverá ser resguardada, do contrário, será preciso anexar-lhes permissão por escrito para divulgação.
16. Os gráficos deverão ser elaborados em Microsoft Excel. As tabelas dispensam sua descrição no texto tendo a finalidade de suplementá-lo e não a de aumentá-lo. As unidades utilizadas para exprimir os resultados (m, g, g/100, mL etc.) figurarão no alto de cada coluna. Os pacientes devem ser identificados por números ou letras, e nunca pelos nomes, iniciais ou número de registro hospitalar.
17. O limite máximo de autores aceitável é de 5; só haverá exceção para trabalhos de maior complexidade (ex. Artigo Original, Revisão) mediante justificativa e aprovação dos editores.
18. As opiniões e declarações contidas na revista são de responsabilidade única e exclusiva de seus autores, não sendo, necessariamente, coincidentes com as da Equipe Editorial, do Conselho de Revisores ou da Sociedade Brasileira de Dermatologia.

Os autores deverão submeter seu manuscrito para avaliação do Conselho Editorial da revista no endereço eletrônico que se segue: http://www.sgponline.com.br/scd/sgp/.

Todos os documentos como Consentimento de uso para publicação (Copyright), Conflito de interesses e Autorização para publicação de fotografias estão disponíveis no site da revista e no sistema de submissão online. Estes documentos devem ser assinados por todos os autores participantes e anexados no sistema ao se submeter o manuscrito. Autorização para publicação de fotografias só se faz necessária quando identifica a face do paciente por completo. O documento de Participação no trabalho só será solicitado pelos editores se houver necessidade.
Contato da revista:

A/C Surgical & Cosmetic Dermatology
Av. Rio Branco, nº 39, 18º andar.
Rio de Janeiro – RJ, Brasil.
CEP: 20090-003.
surgical@sbd.org.br

A revista aceita trabalhos inéditos e não publicados das seguintes categorias:

1 – ARTIGOS DE REVISÃO

Poderão ser aprofundados os temas específicos nas áreas de interesse da S&CD, algoritmos, compilações e estatísticas. Estes trabalhos têm formato livre, porem devem conter resumo não estruturado de até 100 palavras e conclusões ou considerações finais. Limite: texto até 6000 palavras, 10 ilustrações e 60 referências. Os artigos de revisão sistemática ou metanálises devem seguir orientações pertinentes (http://cochrane.bireme.br)

2 – ARTIGO ORIGINAL

É o relato de uma pesquisa investigativa original nas áreas de Cirurgia Dermatológica, Oncologia Cutânea, Tecnologia em Dermatologia e Dermatologia Cosmética. Exemplos: estudos experimentais, estudos clínicos, comparações e descrições de técnicas ou de métodos de avaliação, estudos de áreas afins (ex: estudos farmacêuticos em dermatologia cosmética). O texto deverá conter até 4000 palavras, 10 ilustrações e 35 referências e seguir o formato IMRDC (Introdução e objetivo, Métodos, Resultados, Discussão, Conclusão)

Resumo: deverá conter no máximo 200 palavras e ser estruturado seguindo os itens: Introdução, Objetivo, Métodos, Resultados e Conclusões. Não é permitido afirmar que os resultados ou outros dados serão apresentados ou discutidos.

Introdução: citar as razões que motivaram o estudo, descrevendo o estado atual do conhecimento sobre o tema. Utilizar o último parágrafo para especificar a principal pergunta ou objetivo do estudo, e a principal hipótese testada, se houver.

Métodos: Explicar como o estudo foi feito:

a-Tipo de estudo: descrever o seu desenho especificando a direção temporal (retrospectivo ou prospectivo), o tipo de randomização quando utilizada (pareamento, sorteio, sequenciamento, etc), se o estudo foi cego, comparativo, controlado por placebo, etc.

b- Local: indicar onde o estudo foi realizado (instituição privada ou pública), citar que a pesquisa foi aprovada pelo

Comitê de Ética em Pesquisa de sua instituição, os procedimentos de seleção, os critérios de inclusão e exclusão, e o número inicial de pacientes.

c-Procedimentos: descrever as principais características das intervenções realizadas, detalhando a técnica e lembrando que o estudo de investigação deverá ser reprodutível.

d- Descrição dos **métodos** utilizados para avaliação dos resultados.

e- Inclusão da **análise estatística** descritiva e/ou comparativa com descrição do planejamento da amostra (representativa do universo a ser estudado), a análise e os testes estatísticos e apresentação dos níveis de significância adotados. A utilização de análises estatísticas não usuais é incentivada, porém neste caso, deve-se fazer uma descrição mais detalhada da mesma.

Resultados: descrever os principais resultados que devem ser acompanhados de estimativas pontuais e medidas de dispersão (p.ex., média e erro padrão) ou de estimativas intervalares (p.ex., intervalos de confiança), bem como os níveis descritivos dos testes estatísticos utilizados (p.ex."p-value"). Os achados também devem ser interpretados sob o ponto de vista clínico.

Discussão: enfatizar os novos e importantes resultados encontrados pelo estudo e que farão parte da conclusão. Relatar observações de outros estudos relevantes. Mencionar as limitações dos achados e as implicações para pesquisas futuras.

Conclusões: devem ser concisas e responder apenas aos objetivos propostos. A mesma ênfase deve ser dada para estudos com resultados positivos ou negativos.

3 - COMUNICAÇÕES

Artigos originais, breves, abordando resultados preliminares de novos achados de interesse nas áreas focadas pela revista. Texto com formatação semelhante ao artigo original, resumo estruturado de até 200 palavras. Limite: texto até 2000 palavras, 8 ilustrações e 15 referências.

4 – DIAGNÓSTICO POR IMAGEM

Abordagem de temas ou casos clínicos, em que os exames de imagens (dermatoscopia, microscopia confocal, ultrassom e outros métodos) são fundamentais no diagnóstico ou tratamento. Resumo não estruturado de até 100 palavras, texto até 1200 palavras, 6 ilustrações e 5 referências.

5 – COMO EU FAÇO?

Descrição de novas técnicas ou detalhes de técnicas. Resumo não estruturado de até 100 palavras, introdução com breve revisão de literatura, métodos, resultados, discussão e conclusão. Limite: 1200 palavras, 8 ilustrações e 30 referências.

6 – RELATO DE CASO

Descrição de casos ou serie de casos de relevância nas áreas de interesse da S&CD, com descrição de tratamentos, complicações, etc. Resumo não estruturado de até 100 palavras, introdução com revisão de literatura, métodos, resultados, discussão e conclusão, sempre que pertinentes. Limite: texto até 1200 palavras, 8 ilustrações e 30 referências.

7 – CARTAS

Comentários objetivos e construtivos sobre matérias publicadas ou notas breves. Texto até 600 palavras, 2 ilustrações, e no maximo 5 referências.

Surgical & Cosmetic Dermatology

Table of contents / *Sumário*

Publicação Oficial da Sociedade Brasileira de Dermatologia
JANUARY/FEBRUARY/MARCH 2019 • Volume 11 • Number 1
ISSN:1984-5510
Online ISSN: 1984-8773

Review Articles / *Artigo de Revisão*

Cells biomodulation: the future of Dermatology 11
Biomodulação celular: o futuro da Dermatologia
Carlos Roberto Antonio, Lívia Arroyo Trídico

Original Articles / *Artigos Originais*

Evaluation of the efficacy and safety of microneedling with 5-fluorouracil for the treatment of striae alba: double-blind, randomized clinical trial 19
Avaliação da eficácia e segurança do microagulhamento com 5-fluorouracil para o tratamento de estrias albas: ensaio clínico randomizado duplo-cego
Danielle Claudino de Oliveira Costa, Ada Regina Trindade de Almeida, Maria Victoria Suarez Restrepo, Liliana Bechelli de Oliveira Torloni

The use of photodynamic therapy with methyl aminolevulinate and daylight for the treatmento of actinic keratoses 26
O uso da terapia fotodinâmica com aminolevulinato de metila e luz do dia para tratamento de queratoses actínicas
Thamiris Antonini Marçon, Beatrice Abdalla, Silvia Arroyo Rstom, Carlos D'Apparecida Santos Machado Filho, Francisco Macedo Paschoal

Growth factors and healing: experience in a Dermatology service 31
Fatores de crescimento e cicatrização: experiência em um serviço de Dermatologia
Felipe Siqueira Ramos, Elisangela Manfredini Andraus de Lima, Flávia Regina Ferreira, Samuel Henrique Mandelbaum

Botulinum toxin for the treatment of facial hidrocystomas 35
Toxina botulínica para o tratamento de hidrocistomas faciais
Ada Regina Trindade de Almeida, Jaqueline Guerra, Marcelo Bellini, Alessandra Romiti, Maria Victoria Súarez Restrepo

Civil responsibility and its consequences for the Dermatology practice 41
Responsabilidade civil e suas consequências no exercício da Dermatologia
Valéria Maria de Souza Framil, Erika Tiemi Fukunaga, Eduardo da Costa Sá, Daniel Romero Muñoz

Histologic evaluation of the reduction of cutaneous melanin content after microneedling on the chest 49
Avaliação histológica da redução do conteúdo melânico cutâneo após realização de microagulhamento na região anterior do colo
Luiza Helena Urso Pitassi, Célia Luiza Petersen Vitello Kalil, Clarissa Prieto Herman Reinehr, Valéria Barreto Campos, Christine Chaves, Stela Cignachi

Lysine hydrochloride use in the prophylaxis of herpes simplex in facial technology-aided procedures 55
Uso do cloridrato de lisina na profilaxia do herpes simples nos procedimentos faciais com tecnologias
Victor Bechara de Castro, Maria Eduarda Pires, Paula Regazzi de Gusmão, Alexandre de Almeida Filippo, Manuela da Silva

Diagnostic imaging / *Diagnóstico por imagem*

The use of dermatoscopy of the nail plate and its free margin to aid the diganosis of onychomatricoma 59
O uso da dermatoscopia da placa ungueal e de sua borda livre auxiliando o diagnóstico do onicomatricoma
Eckart Haneke, Nilton Di Chiacchio

Table of contents / *Sumário*

How I do? / *Como eu faço?*

Criobiopsy in dermatological practice 61
Criobiópsia na prática dermatológica
Rachel de Avila Coelho, Luiz Fernando de Oliveira Santana, Juliana Cristina Silva Fraga

Case Reports / *Relatos de Caso*

Treatment of disseminated superficial actinic porokeratosis with 1340-nm Nd:YAP laser 65
Tratamento da poroqueratose actínica superficial disseminada com laser 1340-nm Nd:YAP
Rodolfo Ferreira Mendonça, Lyvia Almeida Nascimento Salem, Renata Oliveira Alves, Bomi Hong, Rute Facchini Lellis, Elisete Isabel Crocco

Giant eccrine spiroadenoma associated to Brooke-Splieger syndrome 68
Espiradenoma écrino gigante associado à síndrome de Brooke-Splieger
Taiane Medeiros Terra, Flavia Tandaya Grandi Miranda, Luiz Fernando Froes Fleury Junior

Treatment of neurofibromatosis NF-1 with CO_2 laser - case report 72
Tratamento de neurofibromatose NF-1 com laser de CO_2 – Relato de caso
Luciane Prado Silva Tavares, Osterno Potenciano,Yasmin Pugliesi, Raissa Lelitscewa da Bela Cruz Faria, Nathalia Lelitscewa da Bela Cruz Potenciano, Lara Silva Paixão

Milia over tattoo: successful conservative treatment 76
Mília sobre tatuagem: tratamento conservador bem-sucedido
Helena Reich Camasmie, Antonio Macedo D'Acri

Letter / *Carta*

The dark side of skin lightening 78
O lado negro dos clareadores cutâneos
Daniela Alves Pereira Antelo

Cells biomodulation: the future of Dermatology

Biomodulação celular: o futuro da Dermatologia

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111325

ABSTRACT

The evolution of medicine has allowed an increasingly in-depth knowledge of diseases and medications, involving cellular structures and associated molecules. In dermatology, we begin to unveil cell modulation associated to the use of substances such as botulinum toxin, hyaluronic acid, among others. This new era allows us to comprehend information that goes beyond a macroscopic view and explore cell interaction, leading to a broader knowledge to optimize dermatologic treatment.

Keywords: Biology; Cells; Dermatology

RESUMO

A evolução da Medicina tem permitido um conhecimento cada vez mais profundo de patologias e medicações envolvendo estruturas celulares e moléculas associadas. Em Dermatologia, começamos a desvendar a modulação celular associada ao uso de substâncias como a toxina botulínica, o ácido hialurônico, entre outros. Esta nova era nos permite compreender informações que vão além de uma visão macroscópica e explorar a interação celular, adquirindo-se conhecimento mais amplo para otimizar a terapêutica dermatológica.

Palavras-Chave: *Biologia; Células; Dermatologia*

INTRODUCTION

The evolution of Medicine over the years has allowed the knowledge of the mechanism of action of diseases and medications in the intra and extracellular levels. The initial knowledge that was restricted to anatomy and a macroscopic view of physiology in many areas of Medicine, is advancing towards cellular microscopy, with better understanding of the intracellular and extracellular structures and many molecules secreted by different parts of a cell. The knowledge on cellular microenvironments allows us to observe the way cells interact and react to the external environment. However, there is still a lot of information to come.

In dermatology, we are also entering a new era once we started to unveil cell modulation associated to the use of nanoparticles and biodegradable substances. Initially, when using substances such as botulinum toxin and hyaluronic acid, we had their macroscopic action as the basic concept, meaning that hyaluronic acid acts occupying space and stimulating collagen, and the toxin acts paralyzing the muscles through acetylcholine blockage at the muscular junction.

Review Articles

Authors:
Carlos Roberto Antonio[1]
Lívia Arroyo Trídico[1]

[1] Dermatologic Surgery, Service of Dermatology, Faculdade de Medicina de São José do Rio Preto - São José do Rio Preto (SP), Brazil.

Correspondence:
Pelle Medical Center
Av Arthur Nonato, 4235
Nova redentora
15090-040, São José do Rio Preto, SP
Brasil
E-mail: latridico@gmail.com

Received on: 18/01/2019
Approved on: 11/02/2019

Study conducted at Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto (SP), Brazil.

Financial support: None.
Conflict of interests: None.

Nowadays, we understand the action of these substances is much broader: it involves cell modulation, i.e., botulinum toxin also acts controlling inflammation, pain, pruritus, among others, whereas hyaluronic acid acts beyond filling since it interacts with adipocytes, fiber networks of the extracellular matrix and mesenchymal stem cells.[1,2]

We know that cells are rarely balanced, and understanding how cellular changes occur are fundamental issues in Cell Biology. There is much to understand about how cells accumulate information on their environment over time and how external stimuli are molecularly translated into cellular decisions. Controlling the environment as much as possible can help answer these questions. The future work should focus in the development of new ways of tracking and observing the cell dynamics over long periods of time. Besides, one must note that the changes do not only take place inside the cells; cells also change their surroundings.

With this study, we aim to comprehend the cellular activity of substances frequently used in Aesthetic Dermatology. With this literature review, we bring information that will allow us to understand their mechanism of action way beyond their macroscopic view, in order to optimize and broaden their use in Dermatology and explore more benefits for our patients.

Botulinum toxin

We know that botulinum toxin blocks the release of acetylcholine and many other pre-synaptic neurotransmitters, deactivating SNARE proteins and providing therapeutic applications in neurologic conditions with safety and efficacy. The skin also interacts with the nervous system and there are increasing evidences that the neurologic system plays a part in cutaneous inflammation and wound healing.[3,4] This way, botulinum toxin has been used in many dermatologic conditions that include prevention of scarring, facial flushing, post-herpetic neuralgia and pruritus, with great results. The mechanism involved in these new indications includes suppression of mast cell activity, inhibition of substance P, peptide related to calcitonin gene and release of glutamate.[5]

There are growing evidences that botulinum toxin (BoNT) shows biologic effects in many types of human cells, with a series of clinical implications associated to its non-neuronal and non-muscular effects. BoNT receptors and intracellular targets are not exclusive for neurotransmission. They have been found in neuronal and non-neuronal cells. Non-neuronal cells that express one or more botulinum toxin binding proteins and/or proteins associated to the synapse cleavage target include: epidermal keratinocytes; subcutaneous fat tissue mesenchymal stem cells; cells of the nasal mucosa; urothelial cells; epithelial intestinal, prostate and alveolar cells; breast cell lineages; neutrophils; and macrophages. BoNT/A serotype can also cause specific biological effects in dermal fibroblasts, sebocytes and vascular endothelial cells.[6]

The use of BoNT in hypertrophic scars and keloids has been associated to the significant reduction of erythema, pruritus, elasticity and size of the scar.[7,8] The molecular mechanism involved in this process encompasses the inhibition of the proliferation of fibroblasts derived from the scar tissue, besides suppression of the expression of the transforming growth factor TGF-beta1, collagen I and II and muscle proteins actin and myosin II in keloid fibroblasts.[5,9,10,11] The symptoms of pruritus and pain are alleviated with the reduction of tension in the skin and local muscles, releasing nerve fibers trapped in the scar.[5]

The prevention of surgical scars and the improvement in their appearance can also be achieved with botulinum toxin. A study performed in patients with thyroidectomy scars, treated 10 days after surgery showed significant improvement in comparison with the group treated with saline 0.9% (control).[12,13] The anti-inflammatory action of botulinum toxin in the cutaneous vascularization reduces the inflammatory phase of the cicatricial process; besides, its action in fibroblasts and in the expression of TGF-beta1 acts improving the appearance of the scar.[5]

Regarding evidences of the action of botulinum toxin for the treatment of rosacea and facial flushing, it is known that BoNT acts inhibiting the release of inflammatory mediators such as the gene related to calcitonin peptide and substance P. Therefore, reduction of the local cutaneous inflammation causes improvement of the erythema. Flushing also improves due to the blockage of the release of acetylcholine from the peripheral nerves of the cutaneous vascular system.[14,15,16]

Post-herpetic neuralgia is a very common complaint due to the neuropathic pain resulting from herpes zoster infection. Botulinum toxin is an effective therapeutic alternative in relation to the main treatments used (anti-inflammatory, gabapentin, opioid and tricyclic antidepressants). The exact mechanism of action of BoNT in post-herpetic neuralgia is still unclear, however, there is the action of peripheral and central mechanisms involved. The peripheral effects are associated to the inhibition of release of neuropeptides from nociceptive peripheral nerves, whilst the central nervous system acts through the transport of peripheral axons (area of application) towards the central.[5, 17,18]

Pruritus, present in many dermatologic conditions, when peripherally induced (pruriceptive pruritus) shows significant improvement with the application of intradermal botulinum toxin.[19] The molecular mechanisms involved in the improvement of pruritus with botulinum toxin are mast cell stabilization and inhibition of its degradation caused by BonT.[20] Furthermore, BonT interacts with substance P, which is associated to the release of histamine by the activation of mast cells and vasodilation. Peripheral pruritus is usually accompanied by cutaneous inflammation in the majority of cases, such as atopic dermatitis and psoriasis. Therefore, the anti-inflammatory capacity of BoNT improves inflammation with subsequent improvement in the pruritus.[5]

The use of botulinum toxin for the treatment of dyshidrosis can be explained by its action in the muscles surrounding the sweat glands and by the inhibition of the release of acetylcholine, which reduces sweating, associated to the inhibition of substance P, which causes reduction in pruritus.[21,22] For hidradenitis, BoNT also acts reducing sweating; as a consequence, it reduces bacterial flora and subsequent inflammation.[23] In Hai-

ley-Hailey disease, there is reduction of sweating, pruritus and inflammation, also associated to the inhibition of acetylcholine and substance P.[5]

Recently, BoNT has been used in the control of skin oiliness.[24,25] Sebum contributes to the delivery of soluble antioxidants in fat on the skin surface and has antimicrobial activity, working as a cutaneous barrier. However, excessive sebum blocks the pores and offers nutrients to bacteria, which can result in inflammation of the skin.[5] The exact mechanism of botulinum toxin in the reduction of sebum is not completely clear, but it is likely that erector pilli muscles and local muscarinic receptors in sebaceous glands are the targets of the neuromodulatory effects of BoNT. It is known that the acetylcholine nicotinic receptor á7 (nAchRá7) is expressed in human sebaceous glands in vivo, and acetylcholine signal enhances the synthesis of lipids in vitro in a dose-dependent fashion.[26]

Lately, there have been evidences of the use of botulinum toxin for the treatment of androgenetic alopecia. In order to understand the mechanism of action involved it is necessary to understand that, in areas affected with hair rarefaction, there is relative hypoxemia, slower capillary filling and high levels of dihydrotestosterone.[27] The enzymatic conversion of testosterone into dihydrotestosterone depends on oxygen. In low concentrations of oxygen, the conversion is favored, leading to increased hair loss, whereas in high concentrations of oxygen, the favored conversion is testosterone into estradiol, favoring reduction of hair loss. Therefore, the application of botulinum toxin in the scalp reduces the vascular pressure when reducing muscular tone, creating increased local vascular flow and, consequently, increased oxygen, which reduces the enzymatic conversion of testosterone into dihydrotestosterone.[28] In a study conducted by Singh *et al* (2018), 10 patients with androgenetic alopecia were treated with five-unit injections of botulinum toxin in 30 points in the scalp; 80% had an excellent improvement in 24 weeks. Only one patient failed the treatment, and another patient showed poor response to treatment, therefore demonstrating the therapeutic efficacy and safety of BoNT in androgenetic alopecia in this pilot study.[29]

Hyaluronic acid

Hyaluronic acid (HA) fillers are widely used in aesthetics due to their efficacy, safety, versatility and low allergenic potential. They are used with the goal of occupying physical space and/or volume enhancing, since it is a hydrophilic material that is also a natural component of the skin. This way, we use hyaluronic acid broadly to rejuvenate, when filling areas of skin atrophy and also in cases of bony resorption, loss of elasticity and fat caused by ageing.[30,31]

However, it is important to understand that the action of hyaluronic acid is broader than just filling spaces, since there are evidences of the interaction between hyaluronic acid and adipocytes, extracellular matrix network and mesenchymal stem cells.[32] Thus, besides filling, HA has cell interactions, participating in biomodulation.

Regardless of the application technique of hyaluronic acid fillers, most of them are knowingly applied into the subcutis.[33,34,35] In the study by Arlette and Trotter (2008), 16 patients that had the nasolabial fold area treated with hyaluronic acid filler and were subsequently submitted to Mohs micrographic surgery with resection of the skin from the nasolabial fold had the specimen histologically analyzed, and in all of them, hyaluronic acid was present in the subcutis with a thickness of 2.1+/-0.6mm (mean dermis thickness of 1.04 to 1.86mm).[33]

Filling creates microtraumas in adipocytes caused by the hyaluronic acid injected, that creates a stress response in the fat tissue. In order to prevent rupture of adipocytes, there is collagen stimulation (induction of fibrillar fibrosis by type I collagen and pericellular fibrosis by type IV and VI collagen).[36] The mechanical stress created by the filler is also one of the factors inducing mesenchymal stem cells derived from the fat tissue, that will encounter a microenvironment favorable for expansion and differentiation, what probably explains the prolonged duration of the filler (up to 12 months).[32]

Adipocytes present in the subcutis control the activity of dermal fibroblasts through the secretion of cytokines. Dermal fibroblasts express receptors for adiponectin and leptin, and both cytokines significantly increase the production of HA by fibroblasts; besides, adiponectin stimulates the production of collagen.[37] Therefore, the activation of mature adipocytes and stem cells is likely to contribute for the effects of HA injections.[32]

Furthermore, there is an interaction between hyaluronic acid and molecules and receptors involved in signal transduction. Molecules such as aggrecan, versican and neurocan and receptors like CD44, RHAMM and TSG6 are examples that illustrate the fact. Due to its wide distribution, CD44 is considered the primary HA receptor in most cells. HA induced a strong proliferative response of fibroblasts and keratinocytes in cell cultures.[38,39]

Turlier *et al* (2013) demonstrated that the injection of hyaluronic acid into the skin caused increase in pro-collagen, in the gene expression of pro-collagen I and III and of matrix metalloproteinase inhibitor-1. Moreover, the activation of fibroblasts was also observed, possibly due to the elongation of its cellular shape.[40] In the study by Wang *et al* (2007), a similar effect was observed on the damaged forearm skin that, after being treated with hyaluronic acid, showed elongation of fibroblasts and increased expression of pro-collagen I and III and of various pro-fibrotic growth factors.[41]

Quan *et al* (2013) studied the buttock skin of elderly patients that were treated with hyaluronic acid fillers. The authors demonstrated elongated fibroblasts adjacent to the deposition of the filler, besides three times the induction of transforming growth factor beta (TGF-beta) and ten times the induction of connective tissue growth factor compared to controls. Improvement in the extracellular matrix promoted fibroblast growth and vascular support.[42]

Poly-L-lactic acid

Poly-L-lactic acid (PLLA) is a synthetic biocompatible and biodegradable polymer produced through fermentation of renewable plant sources. Its clinical effect is due to the stimula-

tion of neocollagenesis. Neocollagenesis caused by poly-L-lactic acid is due to the stimulation of a desired controlled inflammatory response, that leads to the slow degradation of the material and culminates with collagen deposition in the tissue. Once injected in the skin, there is a subclinical inflammatory response with the recruitment of monocytes, macrophages and fibroblasts. A capsule is formed individually around each microsphere. As poly-L-lactic acid is metabolized, the increased collagen deposition produced by the fibroblast remains, with subsequent increase in dermal thickness. Therefore, fibroplasia is a determinant of the cosmetic results, but there is no evidence of residual fibrosis. The production of type I collagen starts around 10 days after the injection and continues for a period that ranges from eight to 24 months, while the product is degraded and the subclinical response fades.[43] Kim *et al* (2019) evaluated the molecular biologic effect of PLLA in the synthesis of collagen and the signaling pathways related through human dermal fibroblast (Hs68) culture in vitro, which were stimulated with PLLA and analyzed regarding expression of the type I collagen gene, induced by the polymer through RT-PCR, Elisa and Western-Blot. The results obtained suggest that PLLA acts directly on dermal fibroblasts. There was up regulation in the expression of the type I collagen gene and in the protein synthesis in the first 48 hours of incubation, a mechanism mediated through the activation of signaling proteins p38, Akt and JNK.[44]

Stein *et al* (2015) evaluated the biological mechanism associated to the use of poly-L-lactic acid through characterization of the cell infiltrate and the type of collagen present in the tissue treated with poly-L-lactic acid, analyzed by immunofluorescence. Macrophages CD68 and fibroblasts CD90 were found around the treated tissue. Structures positive for áSMA indicated myofibroblasts and neovascularization. Deposition of type III collagen was detected close to the PLLA particles and type I collagen was found in the periphery of PLLA encapsulation. The expression of mRNA for type I and III collagen transcription, as well as for TGF-beta1, increased significantly. Thus, the authors concluded the effect induced by PLLA is likely based in the formation of capsules, orchestrating macrophages, myofibroblasts and type I and III collagen fibers.[45]

Goldberg *et al* (2013) evaluated tissue response to PLLA in 14 patients that underwent PLLA injection and, subsequently, were biopsied in the area after 3, 6 and 12 months. In a qualitative and quantitative analysis of the collagen, there were evidences of increased type I collagen 6 months after the treatment. The inflammatory response observed to PLLA was mild or absent, and no patient showed moderate to severe inflammation in the 3, 6 and 12 months biopsies.[46]

Calcium hydroxylapatite

Calcium hydroxylapatite (CaHA)-based fillers are biodegradable and biostimulants. They are composed of two minerals found in bones and teeth (calcium and phosphate), and therefore are biocompatible and non-toxic. Their use was approved by the FDA (Food and Drug Administration) in 2006 for facial filling, being initially used for the correction of moderate and deep wrinkles and for the treatment of lipoatrophy in patients with the human immunodeficiency virus. In view of the good results with CaHa fillers, their off label use expanded to other indications, such as: regeneration of volume in the aged hand, correction of marionette lines, enhancement of volume in the malar, zygomatic and submalar areas, lip augmentation and acne scars. The initially known mechanism of action of CaHA filler involves the distribution of microspheres of calcium hydroxylapatite in soluble gel in the area of injection, which are responsible for promoting collagenesis.[47]

Zerbinat *et al* (2017) evaluated the interaction of CaHA and the extracellular matrix and connective tissue cells. With electron microscopy performed 2 months after filling of abdominal skin with CaHA, more basophilic fibroblasts, high in rough endoplasmic reticulum and electrodense filamentous material were seen, corresponding to the precursors of fibrillar components, particularly collagen, of the extracellular matrix. Besides, a well-developed Golgi apparatus was present, responsible for the synthesis of molecular components of the extracellular matrix (proteoglycans, glycosaminoglycans and multiadherent glycoproteins). These structural changes demonstrate the involvement of stimulated fibroblasts in the production of new molecular components of the extracellular matrix, with active renovation and remodeling of the connective tissue. This renovation of the molecular components of the extracellular matrix increases skin support, creating an additional action, restorative and physiologic of the filler, aesthetically and functionally.[48]

Moreover, scattered microgranular material was also detected in the space of the interstitial matrix, related to the activity of the cells surrounding the microspheres of CaHA. Observations in the interface between the microspheres of CaHA and the adjacent cells, such as the increase in number of invaginations of plasma membranes of these cells, demonstrate an important communication between the filler and surrounding cells. There is probably an active cellular mechanism of enzyme delivery through the surface of the plasma membrane.[48]

Zerbinati and Calligaro (2018) evaluated the effects of CaHA fillers in the molecular arrangement of the collagen, performing a biopsy of the area treated two months after the procedure. With polarized light microscopy, it was shown that the subdermal injection of CaHA stimulates the formation of new collagen and dermal remodeling, with type III collagen neoformation, which is gradually replaced by type I collagen for the support of the optimal structure. Probably, the microspheres of CaHa in the connective tissue provide a tridimensional environment for the adherence of fibroblasts, similarly to the structure of young skin, allowing CaHa to induce biostimulation to the target collagen in the injection site.[49]

Actives for body contouring

The female complaint that the fat in the hips and thighs is harder to mobilize was always common, however, these empirical observations were not initially validated. These observations are now scientifically confirmed, for it is understood that the distribution of fat is determined by the lipolytic thresholds

relative to fat cells in different body areas. We know that a higher number of á-2 adrenergic receptors is found in the fat cells of the hips and thighs in women, and that these á-2 adrenergic receptors inhibit lipolysis. Estrogen increases the number of á-2 receptors in these areas, and it is responsible for the distribution of the gynoid fat of women.[50,51]

Many times, fat reduction in a certain part of the body is not possible under normal conditions because the endogenous lipolytic stimulants, such as catecholamines, reduce all body lipolytic thresholds in the same degree, without creating any relative change between the deposits.[50,51]

Recent studies evaluated factors that regulate and affect the lipolytic process. There are at least three general mechanisms by which lipolysis can be enhanced: inhibition of phosphodiesterase or of the adenosine receptor; activation of the â-adrenergic receptor or inhibition of á-2 receptor. These mechanisms are the basis for lipolytic mesotherapy.[51,52]

Besides lipolytic stimulation to increase lipolysis, another mechanism can be used for lipolysis: the destruction of fat cells using a detergent (ablative mesotherapy). This technique is usually performed using substances such as phosphatidylcholine and sodium deoxycholate.[51,52]

Here, we will report the mechanism of biomodulation of substances used for body contouring improvement through lipolysis:

L-carnitine: amino acid that acts as an essential cofactor for the metabolism of fatty acids, reducing triglycerides and total cholesterol, improving lipid metabolism. It enhances the transportation of fatty acids into the mitochondria, where the process of beta-oxidation occurs (fat breakdown). Its absence prevents this transportation from taking place.[50]

Benzoic caffeine: induces lipolysis via inhibition of phosphodiesterase, what generates an increase in cyclic adenosine monophosphate (cAMP), transforming it in an inactive form, 5'cAMP. cAMP activates the enzyme proteinokinase A and, consequently, hormone-sensitive lipase enzyme (HSL), inducing lipolysis through mobilization of fatty acids and glycerol. It also increases catecholamines (epinephrine), activating the sympathetic nervous system.[50]

Organic silicon: natural component, ingested in the diet, with an important role in bones and connective tissue, however, when in high doses, benefits these tissues even further. Studies evaluated the stimulation of this active when associated to an antioxidant compound, revealing increased expression of mRNA of the enzyme type 2 hyaluronic acid synthetase (HAS2 – responsible for the production of hyaluronic acid), of collagen and elastin. Thus, silicon started to be recommended as a supplement, besides being used in mesotherapy, where it can be used alone or combined to other actives, contributing not only to localized fat, but also to facial rejuvenation.[50,53]

Chrysin: is a flavonoid extracted from the plant *Passiflora caerula*. It has anti-inflammatory properties associated to flavonoids, with an additional activity of potent inhibitor of the enzyme aromatase. Aromatase is the enzyme responsible for the conversion of testosterone into estrogen or DHT, it is present in adipocytes and pre-adipocytes, influencing the distribution of the fat tissue. This way, it is indicated for the treatment of cellulite and localized fat, reducing the inflammatory process and improving the venous return, aiding in the drainage of edemas.[50,51]

Mesoglycan: sulphated polysaccharide compound initially used in vascular disorders associated to thrombotic risk. It acts inhibiting the proliferation of smooth muscle cells of the tunica intima of the endothelium, stimulating the enzyme lipoprotein lipase and inhibiting platelet adhesion, therefore acting as antiatherogenic. It has antithrombotic activity by activation of antithrombin III and heparin cofactor II. It reduces capillary permeability and also has fibrinolytic activity by the induction of systemic fibrinolysis through the stimulation of the tissue plasminogen activator, reducing fibrotic processes. This fibrinolytic mechanism is responsible for its use in aesthetic medicine for the treatment of cellulite, for it allows dissolution of the nodules that cause skin deformity.[50, 51]

Sodium deoxycholate: is a salt derived from bile acids that have lipolytic activity over adipocytes. It acts rupturing adipocyte plasma membrane and emulsifying the fat released, making it excretion possible. It is capable of promoting cellular lysis with irreversible destruction of the adipocyte membrane, what explains its increased action in the fat tissue, when compared to other tissues.[54]

Phosphatidylcholine: is an extract derived from soy, with different functions such as: emulsification of fat through activation of liver enzymes (lipases), breaking them down into fatty acids and glycerol; improvement of hepatic fibrosis and fat build up; regulation of the cholesterol metabolism, because it favors the uptake and transport of cholesterol into the liver, reducing the levels of LDL and triglycerides and increasing HDL. Besides, it is the main plasma membrane phospholipid, with an important action in cell apoptosis, and a precursor of Ach, which when in high concentrations decreases laxity and muscle tone.[50,55]

Tranexamic acid

Tranexamic acid is a plasmin inhibitor used to prevent fibrinolysis, in order to reduce blood loss. It is a synthetic derivative of the amino acid lysine, which effect is to reversibly block the binding sites of lysine in the plasminogen molecule, therefore inhibiting plasminogen activator (PA) from converting plasminogen into plasmin. In dermatology, it has been used for the treatment of melasma in various presentations: oral, topical and intradermal injection. Although plasminogen also exists in the human epidermal basal cells, and it is known that cultivated human keratinocytes produce PA, there is a basic explanation that tranexamic acid could affect keratinocyte functions and interactions.[56]

Ultraviolet radiation (UV) induces the synthesis of plasminogen activator and increases plasmin activity in keratinocytes. As a result of plasmin activity, there is intracellular release or arachidonic acid, a precursor of prostanoids, and elevation of the alpha-melanocyte stimulating hormone. These two substances can activate melanin synthesis. Therefore, the antiplasmin activity of tranexamic acid is considered to be the main mechanism of this agent's bleaching effect.[56]

Precursors of plasmin-activated secretory phospholipase take part in the production of arachidonic acid, which is a prostaglandin E2 and leukotriene LK precursor, involved in melanogenesis. Plasmin also participates in the release of basic fibroblast growth factor (FGF), which a potent melanocyte growth factor. Therefore, it is believed that tranexamic acid inhibits plasmin activity in the keratinocyte activated by UV radiation, inhibiting plasminogen binding to the keratinocyte, resulting in a reduced ability of prostaglandin production and subsequent reduction of melanogenesis.[57]

Furthermore, tranexamic acid is similar to tyrosine, partly because of its structure, and can competitively inhibit the activity of the enzyme tyrosinase. There was a significant reduction of tyrosinase activity, of the protein related to tyrosinase TRP1/2 and melanin content in melanocyte culture after 48 hours after adding tranexamic acid in the culture medium irradiated with UVB.[58]

In the study by Kim *et al* (2016), suppression of the paracrine melanogenic factor ET-1 was demonstrated with tranexamic acid, which is increased in melasma patients. ET-1, believed to be secreted by keratinocytes, is a well-known melanogenic factor that induces pigmentation and tanning response to radiation.[59]

Literature reports also suggest that tranexamic acid reduces erythema in melasma skin, because it is associated to a reduce number of vessels in the dermis; therefore, the antiangiogenic effect of tranexamic acid is also considered. The number of vessels and the expression of vascular endothelial growth factor are reduced after using tranexamic acid.[59]

Mast cells are related to many histological changes associated to melasma. Repetitive UV radiation increases the number of mast cells and mast cell tryptase, and tryptase degrades type IV collagen. Mast cells also perform an important role in the development of solar elastosis, one of the histological features of melasma. The amount of elastin in the skin exposed to UV radiation correlates to the mast cell count. Besides, rats with no mast cells do not develop solar elastosis after repetitive UV radiation. Moreover, mast cells can also induce vascular proliferation secreting many angiogenic factors, such as VEGF, FGF-2 and transforming growth factor beta. Tranexamic acid was capable of reducing the activity and number of mast cells in melasma patients.[60]

CONCLUSION

Understanding the mechanisms involved in cell biomodulation is fundamental to understand the use of substances in dermatology with a broader view. Till present, what we know is very limited in view of the magnitude that encompasses biomodulation, a field with recent and growing discoveries. This way, with this review, we aimed at bringing information on this new way of understanding dermatology: biomodulation. ●

REFERENCES

1. Antonio CR, Antonio JR, Trídico LA, Fernandes TEA. Botulinum toxin: a review of its applicability in diseases within the reach of dermatologists. Surg Cosmet Dermatol. 2014;6(3):268-76.
2. Wollina U. Midfacial rejuvenation by hyaluronic acid fillers and subcutaneous adipose tissue - A new concept. Medical Hypotheses. 2015;84(4):327-30.
3. Steinhoff M, Stander S, Seeliger S, Ansel JC, Schmeiz M, Luger T. Modern aspects of cutaneous neurogenic inflammation. Arch Dermatol. 2003;139(11):1479-88.
4. Ansel JC, Kaynard AH, Armstrong CA, Olerud J, Bunnett N, Payan D. Skin-nervous system interactions. J Investig Dermatol. 1996;106(1):198-204.
5. Kim YS, Hong ES, Kim HS. Botulinum Toxin in the Field of Dermatology: Novel Indications. Toxins (Basel). 2017;9(12):E403.
6. Grando SA, Zachary CB. The non-neuronal and nonmuscular effects of botulinum toxin: an opportunity for a deadly molecule to treat disease in the skin and beyond. Br J Dermatol. 2018;178(5):1011-9.
7. Elhefnawy AM. Assessment of intralesional injection of botulinum toxin type A injection for hypertrophic scars. Indian J Dermatol Venereol Leprol. 2016;82(3):279-83.
8. Zhibo X, Miaobo Z. Intralesional botulinum toxin type A injection as a new treatment measure for keloids. Plast Reconstr Surg. 2009;124(5):275e-7e.
9. Xiao Z, Zhang M, Liu Y, Ren L. Botulinum toxin type A inhibits connective tissue growth factor expression in fibroblasts derived from hypertrophic scar. Aesthet Plast Surg. 2011:35(5);802-7.
10. Chen M, Yan T, Ma K, Lai L, Liu C, Liang L, et al. Botulinum toxin type a inhibits alpha-smooth muscle actin and myosin II expression in fibroblasts derived from scar contracture. Ann Plast Surg. 2016;77(3)e46-9.
11. Jeong HS, Lee BH, Sung HM, Park SY, Ahn DK, Jung MS, et al. Effect of botulinum toxin type a on differentiation of fibroblasts derived from scar tissue. Plast Reconstr Surg. 2015;136(2):171e-8e.
12. Kim YS, Lee HJ, Cho SH, Lee JD, Kim HS. Early postoperative treatment of thyroidectomy scars using botulinum toxin: A split-scar, double-blind, randomized controlled trial. Wound Repair Regen. 2014;22(5):605-12.
13. Gassner HG, Brissett AE, Otley CC, Boahene DK, Boggust AJ, Weaver AL, et al. Botulinum toxin to improve facial wound healing: A prospective, blinded, placebo-controlled study. Mayo Clin Proc. 2006;81(8):1023-8.
14. Carmichael MM, Dostrovsky JO, Charlton MP. Peptide-mediated transdermal delivery of botulinum neurotoxin type A reduces neurogenic inflammation in the skin. Pain. 2010;149(2):316-24.
15. Kellogg Jr DL. In vivo mechanisms of cutaneous vasodilation and vasoconstriction in humans during thermoregulatory challenges. J Appl Phys. 2006;100(5):1709-18.
16. Kellogg Jr DL, Pergola PE, Piest KL, Kosiba WA, Crandall M, Johnson JM. Cutaneous active vasodilation in humans is mediated by cholinergic nerve cotransmission. Circ Res. 1995;77(6):1222-8.
17. Ding XD, Zhong J, Liu YP, Chen HX. Botulinum as a toxin for treating post-herpetic neuralgia. Iran Public Health. 2017;46(5):608-11.
18. Apalla Z, Sotiriou E, Lallas A, Lazaridou E, Ioannides D. Botulinum toxin a in postherpetic neuralgia: A parallel, randomized, double-blind, single-dose, placebo-controlled trial. Clin J Pain. 2013;29(10):857-64.
19. Akhtar N, Brooks P. The use of botulinum toxin in the management of burns itching: Preliminary results. Burns. 2012;38(8):1119-23.
20. Park TH.The effects of botulinumtoxin A on mast cell activity: Preliminary results. Burns. 2013;39(4):816-7.
21. Humm AM, Pabst C, Lauterburg T, Burgunder JM. Enkephalin and aFGF are differentially regulated in rat spinal motoneurons after chemodenervation with botulinum toxin. Exp Neurol. 2000;161(1):361-72.
22. Ishikawa H, Mitsui Y, Yoshitomi T, Mashimo K, Aoki S, Mukuno K, et al. Presynaptic effects of botulinum toxin type A on the neuronally evoked response of albino and pigmented rabbit iris sphincter and dilator muscles. Jpn J Opthalmol. 2000;44(2):106-9.
23. O'Reilly DJ, Pleat JM. Richards AM. Treatment of hidradenitis suppurativa with botulinum toxin A. Plast Reconstr Surg. 2005;116(5):1575-6.
24. Min P, Xi W, Grassetti L, Trisliana Perdanasari A, Torresetti M, Feng S, et al. Sebum production alteration after botulinum toxin type A injections for the treatment of forehead rhytides: A prospective randomized double-blind dose-comparative clinical investigation. Aesthet Surg J. 2015;35(5):600-10.
25. Rose AE, Goldberg DJ. Safety and efficacy of intradermal injection of botulinum toxin for the treatment of oily skin. Dermatol. Surg. 2013;39(3 pt 1):443-8.
26. Li ZJ; Park SB, Sohn KC, Lee Y, Seo YJ, Kim CD, et al. Regulation of lipid production by acetylcholine signalling in human sebaceous glands. J Dermatol Sci. 2013;72(2):116-22.
27. Freund BJ, Schwartz M. Treatment of male pattern baldness with botulinum toxin: a pilot study. Plast Reconstr Surg. 2010;126(5):246e-8e.
28. Campanati A, Martina E, Giuliodori K, Consales V, Bobyr I, Offidani A.Botulinum Toxin Off-Label Use in Dermatology: A Review. Skin Appendage Disord. 2017;3(1):39-56.
29. Singh S, Neema S, Vasudevan B. A Pilot Study to Evaluate Effectiveness of Botulinum Toxin in Treatment of Androgenetic Alopecia in Males. J Cutan Aesthet Surg. 2017;10(3):163-7.
30. Goldman A, Wollina U. Facial rejuvenation for middle-aged women: a combined approach with minimally invasive procedures. Clin Interv Aging. 2010;5:293-9.
31. Burgess CM. Principles of soft tissue augmentation for the aging face. Clin Interv Aging. 2006;1(4):349-55.
32. Wollina U. Midfacial rejuvenation by hyaluronic acid fillers and subcutaneous adipose tissue--a new concept. Med Hypotheses. 2015;84(4):327-30.
33. Arlette JP, Trotter MJ. Anatomical localization of hyaluronic acid filler material injected into nasolabial fold: a histologic study. Dermatol Surg. 2008;34(Suppl 1):S56-62.
34. Greco TM, Eelenitsas R. Localization and histological characterization of injected hyaluronic acid in excised nasolabial fold tissue. J Drugs Dermatol. 2010;9(4):399-404.
35. Wortsman X, Wortsman J, Orlandi C, Cardenas G, Sazunic I, Jemec GB. Ultrasound detection and identification of cosmetic fillers in the skin. J Eur Acad Dermatol Venereol. 2012;26(3):292-301
36. Schäffler A, Büchler C. Concise review: adipose tissue-derived stromal-cells--basic and clinical implications for novel cell-based therapies. Stem Cells. 2007;25(4):818-27.
37. Ezure T, Amano S. Adiponectin and leptin up-regulate extracellular matrix production by dermal fibroblasts. Biofactors. 2007;31(3-4):229-36.
38. Fakhari A, Berkland C. Applications and emerging trends of hyaluronic acid in tissue engineering, as a dermal filler and in osteoarthritis treatment. Acta Biomater. 2013;9(7):7081-92.
39. Wohlrab J, Wohlrab D, Neubert RH. Comparison of noncross-linked and cross-linked hyaluronic acid with regard to efficacy of the proliferative activity of cutaneous fibroblasts and keratinocytes in vitro. J Cosmet Dermatol.2013;12(1):36-40.
40. Turlier V, Delalleau A, Casas C, Rouquier A, Bianchi P, Alvarez S, et al. Association between collagen production and mechanical stretching in dermal extracellular matrix: in vivo effect of cross-linked hyaluronic acid filler. A randomised, placebo-controlled study. J Dermatol Sci. 2013;69(3):187-94.

41. Wang F, Garza LA, Kang S, Varani J, Orringer JS, Fisher GJ, et al. In vivo stimulation of de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in hotodamaged human skin. Arch Dermatol. 2007;143(2):155-63.
42. Quan T, Wang F, Shao Y, Rittié L, Xia W, Orringer JS, et al. Enhancing structural support of the dermal microenvironment activates fibroblasts, endothelial cells, and keratinocytes in aged human skin in vivo. J Invest Dermatol. 2013;133(3):658-67.
43. Haddad A, Kadunc BV, Guarnieri C, Noviello JS, Cunha MG, Parada MB. Current concepts in the use of poly-L-lactic acid for facial rejuvenation: literature review and practical aspects. Surg Cosmet Dermatol. 2017;9(1):60-71.
44. Kim SA, Kim HS, Jung JW, Suh SI, R YW. Poly-L-lactic acid increases collagen gene expression and synthesis in cultured dermal fibroblast (Hs68) trough the p38 MAPK pathway. Ann Dermatol. 2019;31(7):97-100.
45. Stein P, Vitavska O, Kind P, Hoppe W, Wieczorek H, Schürer NY. The biological basis for poly-L-lactic acid-induced augmentation. J Dermatol Sci. 2015;78(1):26-33.
46. Goldberg D, Guana A, Volk A, Daro-Kaftan E. Single-arm study for the characterization of human tissue response to injectable poly-L-lactic acid. Dermatol Surg. 2013;39(6):915-22.
47. Pavicic T. Calcium hydroxylapatite filler: an overview of safety and tolerability. J Drugs Dermatol. 2013;12(9):996-1002.
48. Zerbinati N, D'Este E, Parodi PC, Calligaro A. Microscopic and ultrastructural evidences in human skin following calcium hydroxyapatite filler treatment. Arch Dermatol Res. 2017;309(5):389-96.
49. Zerbinati N, Calligaro A. Calcium hydroxylapatite treatment of human skin: evidence of collagen turnover through picrosirius red staining and circularly polarized microscopy. Clin Cosmet Investig Dermatol. 2018;11:29-35.
50. Kutlubay Z. Evaluation of mesotherapeutic injections of three diferente combinations of lipolytic agents for body contouring. J Cosmet Laser Ther. 2011;13(4):142-53.
51. Vanzin SB, Camargo CP. Entendendo ativos coadjuvantes no tratamento da celulite e gordura localizada. Entendendo cosmecêuticos: diagnósticos e tratamentos. 2. ed. São Paulo: Santos, 2011. p. 299.
52. Herreros FO, Moraes AM, Velho PE. Mesotherapy: a bibliographical review. An Bras Dermatol. 2011;86(1):96-101.
53. Deglesne PA, Arroyo R, Fidalgo López J, Sepúlveda L, Ranneva E, Deprez P. In vitro study of RRS® Silisorg CE Class III medical device composed of silanol: effect on human skin fibroblasts and its clinical use. Med Devices (Auckl). 2018;11:313-320.
54. Shridharani SM. Early Experience in 100 Consecutive Patients With Injection Adipocytolysis for Neck Contouring With ATX-101 (Deoxycholic Acid). Dermatol Surg. 2017;43(7):950-958
55. Perez Atamoros FM, Alcala Perez D, Asz Sigall D, Ávila Romay AA, Barba Gastelum JA, de la Peña Salcedo JÁ, et al. Evidence-based treatment for gynoid lipodystrophy: A review of the recent literature. J Cosmet Dermatol. 2018;17(6):977-83.
56. Taraz M, Niknam S, Ehsani AH. Tranexamic acid in treatment of melasma: A 6comprehensive review of clinical studies. Dermatol Ther. 2017;30(3).
57. Tse TW, Hui E. Tranexamic acid: an important adjuvant in the treatment of melasma. J Cosmet Dermatol. 2013;12(1):57-66.
58. 58. Seong JS, Sung HC, Wan IC, Jung MS, Ro SW, Kim MN. Effect of Trans-4-Aminomethylcyclohexanecarboxylic acid on the proliferation and melanization in cultured normal human melanocytes. Ann Dermatol 2007;19(2):60-7.
59. Kim SJ, Park JY, Shibata T, Fujiwara R, Kang HY. Efficacy and possible mechanisms of topical tranexamic acid in melasma. Clin Exp Dermatol. 2016 ;41(5):480-5.
60. Na JI, Choi SY, Yang SH, Choi HR, Kang HY, Park KC. Effect of tranexamic acid on melasma: a clinical trial with histological evaluation. J Eur Acad Dermatol Venereol. 2013;27(8):1035-9.

DECLARATION OF PARTICIPATION:

Carlos Roberto Antonio | ORCID 0000-0001-9243-8293
Design and planning of the study; preparation and writing of the manuscript; critical literature review; critical review of the manuscript.

Lívia Arroyo Trídico | ORCID 0000-0002-7743-4195
Design and planning of the study; preparation and writing of the manuscript; critical literature review; critical review of the manuscript.

Evaluation of the efficacy and safety of microneedling with 5-fluorouracil for the treatment of striae alba: double-blind, randomized clinical trial

Avaliação da eficácia e segurança do microagulhamento com 5-fluorouracil para o tratamento de estrias albas: ensaio clínico randomizado duplo-cego

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111272

ABSTRACT

Introduction: Stretch marks are an everyday challenge to the dermatologist. In the search for alternative therapies, 5-fluorouracil (5-FU) and microneedling emerge for associating the following properties: inhibition of fibrosis, stimulation of collagen renovation and induction of skin pigmentation.

Objective: To evaluate the efficacy and safety of 5-FU, in isolation or associated to microneedling, for the treatment of white stretch marks (striae alba).

Methods: Comparative, double-blind study over 180 days, between 3 groups: Group A: microneedling and 5-FU; Group B intralesional 5-FU and Group C microneedling without medication. We measured improvement through a numerical scale of skin coloration, considering positive results those with reduction of the discrepancy between the adjacent skin and the stretch mark. We also evaluated patient satisfaction and irritation with each technique.

Results: Group A achieved 10% of excellent clinical improvement, 10% very good and 60% mild. In group B, none of the patients had excellent of very good improvement. In group C, there was 20% of very good clinical improvement and 70% of mild.

Conclusions: All techniques showed some degree of improvement of the lesions. Therefore, we propose new studies comparing all three techniques, with a larger sample, to evaluate if more treatments would result in better results.

Keywords: Cosmetic Techniques; Fluorouracil; Striae Distensae; Therapeutics

RESUMO

Introdução: *Estrias são um desafio cotidiano ao dermatologista. Na busca por terapias alternativas, surgem o 5-fluorouracil (5-FU) e o microagulhamento ao associarem as seguintes propriedades: inibir fibrose, estimular renovação do colágeno e induzir pigmentação da pele.*

Objetivo: *Avaliar a eficácia e segurança do 5-FU, isolado ou associado ao microagulhamento, no tratamento das estrias albas.*

Métodos: *Estudo duplo-cego comparativo, durante 180 dias, entre três grupos: Grupo A - microagulhamento e 5-FU; Grupo B - 5-FU intralesional; e Grupo C - microagulhamento sem medicação. Mensurou-se a melhora por meio de uma escala numérica de coloração da pele, considerando-se resultados positivos aqueles com redução da discrepância entre a cor da pele adjacente e a da estria. Avaliou-se também a satisfação do paciente e a irritação com cada técnica.*

Resultados: *Grupo A obteve 10% de melhora clínica excelente; 10%, muito boa; e 60%, leve. No grupo B, nenhuma paciente teve melhora excelente ou muito boa. Já no grupo C, observaram-se 20% de melhora clínica muito boa e 70% de melhora leve.*

Conclusões: *Todas as técnicas apresentaram algum grau de melhora das lesões. Assim, propõem-se novos estudos comparando-se as três técnicas, com amostra mais ampla, para avaliar se maior número de sessões resultaria em resultados mais expressivos.*

Palavras-Chave: *Estrias de Distensão; Fluoruracila; Técnicas cosméticas; Terapêutica*

Original Articles

Authors:
Danielle Claudino de Oliveira Costa[1]
Ada Regina Trindade de Almeida[2]
Maria Victoria Suarez Restrepo[3]
Liliana Bechelli de Oliveira Torloni[1]

[1] Dermatology Clinic, Hospital do Servidor Público Municipal de São Paulo, São Paulo (SP), Brazil.
[2] Cosmiatry Outpatient Department, Dermatology Clinic, Hospital do Servidor Público Municipal de São Paulo, São Paulo (SP), Brazil.
[3] Psoriasis Outpatient Department, Dermatology Clinic, Hospital do Servidor Público Municipal de São Paulo, São Paulo (SP), Brazil.

Correspondence:
Danielle Claudino de Oliveira Costa
Rua Castro Alves, nº 60 - 5° andar - sala 52 - Aclimação
01532-000, São Paulo, SP
Brasil
E-mail: daniellecosta2@hotmail.com

Received on: 22/10/2018
Approved on: 04/01/2019

Study conducted at the institution: Hospital do Servidor Público Municipal de São Paulo, São Paulo (SP), Brazil.

Financial support: None.
Conflict of interestss: None.

INTRODUCTION

Stretch marks are linear dermal scars associated to epidermal atrophy.[1] It is a common clinical condition, prevalent in up to 80% of the population, being 2.5 times more frequent in females.[2] Despite the high prevalence, little attention is given to this condition due to the absence of clinical impact. However, it represents an important cause for cosmetic concern, psychological and social stress.[1,2]

The pathophysiology is still unknown, but endocrine and genetic factors, as well as stretching of the skin are reported as triggers.[3] It is believed the mechanical skin distension generates rupture of dermal elastic fibers. Local fibroblasts cannot reestablish the components of the extracellular matrix and the disorganization of collagen and elastic fibers contributes to the atrophic appearance of striae.[3,4]

In face of the multiple etiologic factors involved, the literature is conflicting and broad regarding treatment. Among the therapies, the most used are topical medications (retinoic acid, moisturizing creams, daily application of glycolic acid and/or peels), combined UVB/UVA1 phototherapy, lasers, microdermabrasion, radiofrequency, intradermotherapy and microneedling.[5,6] We highlight that all existing options are usually costly and require prolonged treatment times.[5]

Microneedling utilizes a system with microneedles applied to the skin, with the goal of creating multiple micro-punctures, deep enough to reach the dermis. The injury would stimulate the expression of different growth factors in the skin (endothelial vascular growth factor, fibroblast growth factor and epidermal growth factor) and the synthesis of type I and III collagen, that promote remodeling of the extracellular matrix.[6,7] This way, microneedling has a broad spectrum of indications when the objective is to stimulate collagen production. Many studies demonstrated this technique to be effective for the treatment of fine and medium wrinkles, skin laxity, facial rejuvenation and correction of scars, as well as improvement of old and early stretch marks.[6,7,8]

5-fluorouracil (5-FU) is a pyrimidine analogue that acts inhibiting the activity of the enzyme thymidylate synthase, that catalyzes the methylation of deoxyurydilic acid into thymidylic acid, interfering in DNA synthesis. Based in this property, this medication is widely used for the topical treatment of actinic keratoses, basal cell carcinomas and plane warts, being the intralesional application indicated for the treatment of keloids, hypertrophic scars and contractures.[9,10,11] Moreover, this drug reduces the risk of excessive cicatricial fibrosis because it inhibits fibroblast proliferation and, due to this feature, is used in many surgeries such as, for example, glaucoma and tendon repair.[12]

Besides, experimental studies obtained relevant information on the biologic impact of this medication in melanocytes. In the presence of a low concentration of 5-FU, keratinocytes are selectively destroyed within 3 weeks, whereas melanocytes continue to multiply and form pigment.[13] Based on this and other studies, 5-FU is also used for the treatment of vitiligo.[14]

According to Fulton *et al*, hypopigmented scars can repigment after mechanical removal of the dermal fibrosis.[15,16] Consequently, Arbache *et al* described repigmentation of idiopathic guttate hypomelanosis after treatment with microneedling associated to 5-FU. With the help of biopsies, it was also verified that, after the procedure, there was an increase in the number of melanocytes, eliminating the possibility of post-inflammatory hyperpigmentation.[17]

There are no previous studies mentioning intralesional 5-fluorouracil or associated to microneedling to treat striae alba. However, this medication is successfully used in the treatment of scars, that have similar anatomopathological features to stretch marks, besides stimulant the production of pigment by melanocytes. Therefore, based on these properties, we opted for this drug in an attempt to improve the clinical appearance of striae alba, reducing the contrast between the adjacent skin and the involved skin.

Thus, this pilot study was conducted to evaluate the efficacy and safety of the association between the two techniques for the treatment of striae alba, comparing it to each technique alone.

METHODS

Design

It is a randomized, double-blind, controlled clinical trial. Eighteen patients, phototype III, IV and V with striae alba located on both buttocks, seen at the Dermatology Clinic of the Hospital do Servidor Público Municipal de São Paulo, in December 2016, who signed the consent form, were selected.

Patients who received previous treatment for stretch marks in the 6 months prior, those with malignancies, cutaneous infection and personal history of keloids, pregnant and breast-feeding, with a history of allergy or hypersensitivity to 5-fluorouracil and those using systemic retinoids, topical or systemic steroids and immunosuppressant medications were excluded.

Randomization

The right and left buttock of the patients were randomized and allocated into three groups: group A (treatment with microneedling and 5-fluorouracil), group B (treatment with intralesional 5-fluorouracil) and group C (microneedling with no medication). The list of randomization was revealed only to the investigator responsible for the treatment, and improvement criteria were evaluated by a blinded observer.

Description of the techniques

An area of 10cm² was selected on each buttock, with higher density of stretch marks for the implementation of the treatment methods. In the same patient, the area was symmetrical bilaterally; only the site varied between patients.

All techniques were performed only once with topical anesthetic. In the groups receiving 5-FU, a maximum dose of 150mg (3ml) was used per area.

In group A, an electrical pen with a multi-needle tip (five needles), Dermograph Dermo Mag (*Anvisa* record number 80815530001) was used, which was dipped into a sterile con-

tainer with 5-FU, absorbing the product by capillarity, and used to create micropunctures along the stretch mark. The pen was dipped into the container and back to the stretch mark many times until the whole extension of the lesion showed pinpoint bleeding and purpuric appearance.

Group B was treated with the injection of 5-FU along the stretch mark, in the dermis, through multiple punctures (0.1ml per puncture) with a 1-cm distance, using insulin syringes (1ml) and 30G needles. The same pen was used in group C to create multiple micropunctures along the stretch mark, with no added local medication, with the same endpoint of the first group.

Visits

The study included five visits on days zero, 2, 30, 90 and 180. On day zero, the selected techniques were applied and the photographic record prior to the procedure was made, as well as on the intermediate visits. On day 180, the efficacy and patient satisfaction with the treatment were evaluated.

Variables analyzed

Clinical evaluation of the lesions regarding the adjacent skin:

The stretch mark on the selected area, and the neighboring skin with no lesions were numbered separately, based on a numerical scale of skin color (Figure 1). The difference between the 2 numbers indicated one discrepancy between the healthy and injured skin (stria alba). Results were considered positive when there was a reduction in the difference between the 2 initial numbers, which were analyzed as follows:

Excellent: the stretch mark achieved the same skin tone as the adjacent normal skin.

Very good: the stretch mark achieved 1 point below the tone of the adjacent normal skin.

Good: the stretch mark achieved 2 points below the tone of the adjacent normal skin.

Mild: achieved less than 2 tones below the tone of the normal adjacent skin.

No improvement: it remained as in the beginning.

Worsening: achieved 1 or more skin tones below the initial color of the stretch mark (hypopigmentation).

Hyperpigmentation: achieved 1 or more tones above the tone of the normal adjacent skin.

Evaluation of the improvement by the patient

The participant answered to the following question: how do you qualify the result of the treatment performed in each buttock? The patients could answer if it was very good, good, mild, no improvement or worse.

Evaluation of the subjective irritation parameters

The parameters burning sensation, pruritus and erythema were evaluated by the participant of the study together with the investigator through a scale ranging from zero to three, considering the lowest score as absence of symptom and the highest as severe symptom.

Statistical analysis

An exploratory analysis was performed through means, frequencies and percentages. Results were compared with the chi-square test or the nonparametric test of Kruskal-Wallis, followed by the procedure of multiple comparisons of Dunn. The level of significance of 5% was considered.

RESULTS

In this study, 15 patients finalized the protocol and were evaluated according to the treatment received. The three excluded participants did not attend the scheduled visits. The incomplete balanced block design was used, i.e., each treatment was applied in 10 buttocks (right or left).

The age group of the participants ranged from 18 to 50 years, with a mean of 35 years. The main cause for the appearance of the stretch marks was weight gain (53.3%), followed by weight loss (13.3%). Other causes reported were steroid use and pregnancy.

Regarding the tone difference between the adjacent skin and the stretch mark in the first visit, it was at least 6 tones in 24 buttocks and at least 3 in 6 buttocks.

Clinical evaluation of the lesions

Of the 10 buttocks treated with microneedling+5-FU, an excellent improvement was seen in 10% (one buttock) and

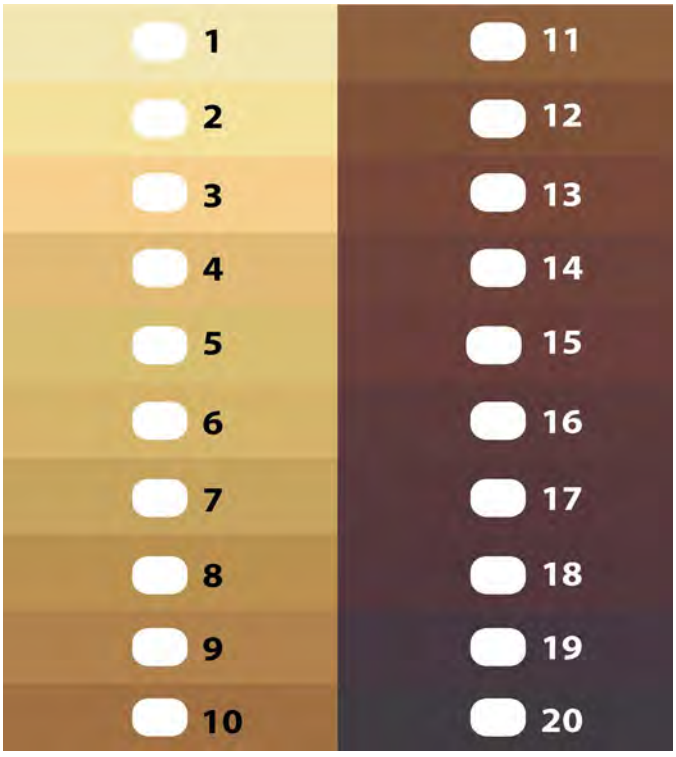


FIGURE 1: Scale of classification of skin color levels

very good in 10% (one buttock). The group treated with microneedling alone achieved 20% (two buttocks) very good response and none with excellent improvement. Regarding 5-FU alone, 20% (two buttocks) showed good response, but none was excellent or very good. However, most buttocks treated with the different techniques showed mild improvement, with 60% (six buttocks) with microneedling+5-FU; 70% (seven buttocks) with microneedling; and 70% (seven buttocks) with 5-FU alone (Graph 1).

The percentage of patients with therapeutic failure was 20% (two buttocks) for the treatment of microneedling +5-FU, due to the absence of clinical improvement and the presence of hyperpigmentation maintained after 6 months of follow up. With the other techniques, there was 10% (one buttock) of therapeutic failure due to lack of clinical improvement.

A significant association between clinical improvement (defined as excellent of very good response) and the treatments evaluated (chi-square; p-value=0.315) was not found.

Figures 2, 3 and 4 illustrate the best results obtained with each technique applied in this study.

Patient satisfaction

We observed that patient satisfaction for treatments with microneedling with or without 5-FU was considered very good for 40% (four), good for 50% (five) and mild for 10% (one). As for treatment with 5-FU alone, 20% (two) considered it very good, 60% (six) good and 20% (two) mild (Graph 2). A significant association between patient satisfaction and the treatments evaluated (chi-square; p=0.840) was not found.

Parameters of subjective irritation

A significant difference between treatments regarding burning sensation on day two was found (Kruskal-Wallis; p=0.049). Burning sensation with treatment with microneedling+5- FU was significantly superior to the treatment with 5-FU alone. The difference for the treatment of microneedling alone in comparison to the others was not significant. On days 30, 90 and 180 there was no burning sensation for any of the treatments evaluated (Graph 3).

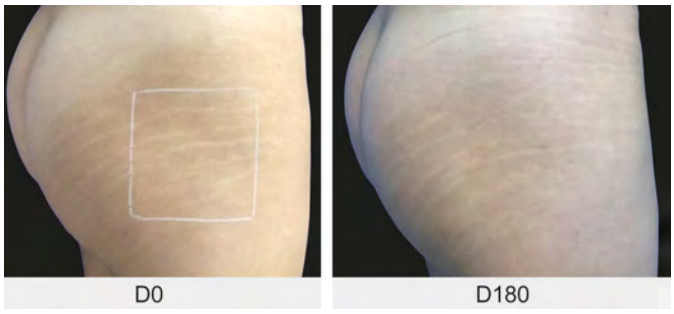


Figure 2: Image showing an excellent response with microneedling + 5-FU

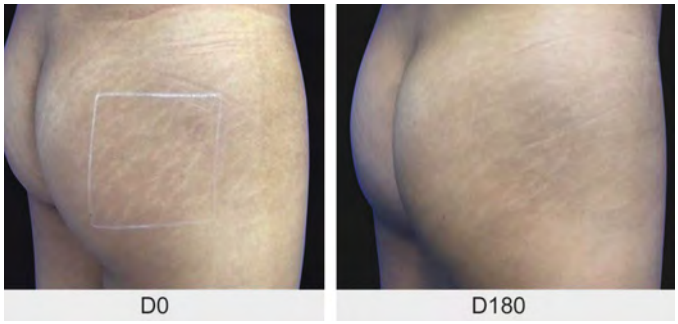


Figure 3: Image showing a good response with intralesional 5-FU

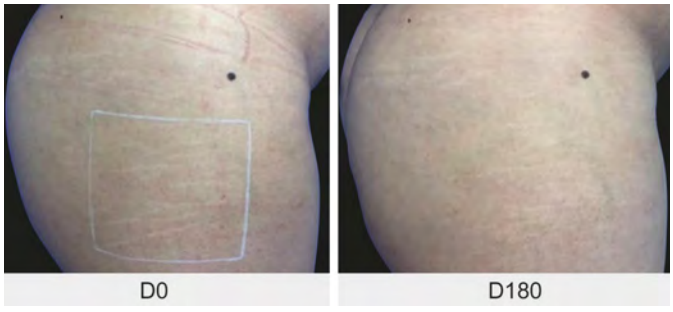
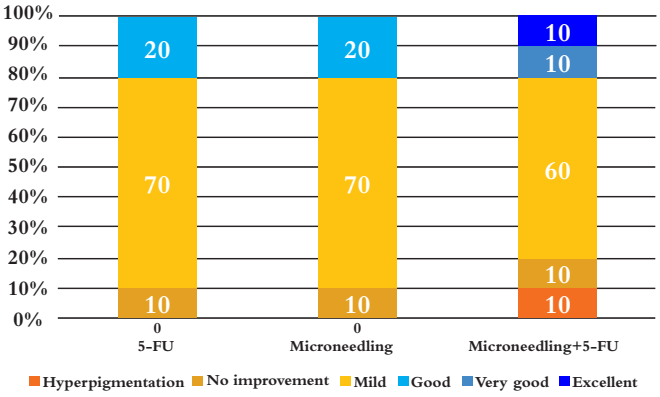
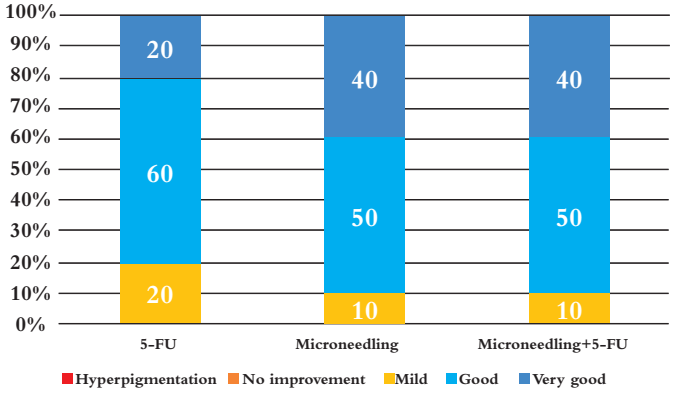


Figure 4: Image showing a very good response with microneedling alone



Graph 1: Percentages of results for the clinical evaluation of lesions per treatment



Graph 2: Percentages of results for patient satisfaction per treatment

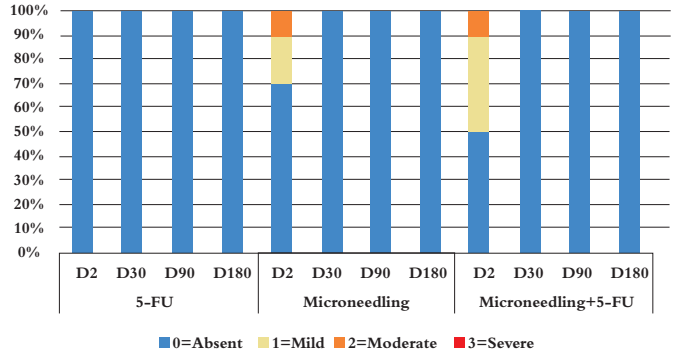
No statistically significant difference was seen between treatments regarding pruritus on day 2 (Kruskal-Wallis; p=0.167) and on day 30 (Kruskal-Wallis; p=0.547). On days 90 and 180, there was no pruritus for any of the treatments evaluated (Graph 4).

A significant difference was seen between treatments regarding erythema

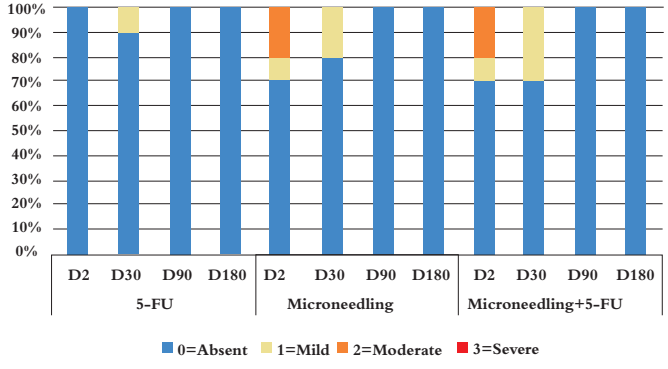
On day 2 (Kruskal-Wallis; p<0.001). The erythema of the treatments with microneedling (microneedling and microneedling+5-FU) was significantly superior to the treatment with 5-FU alone. On day 30, there was no significant difference between treatment (Kruskal- l-Wallis; p=0.212). On days 90 and 180, there was no erythema for any of the treatments evaluated (Graph 5).

Adverse events

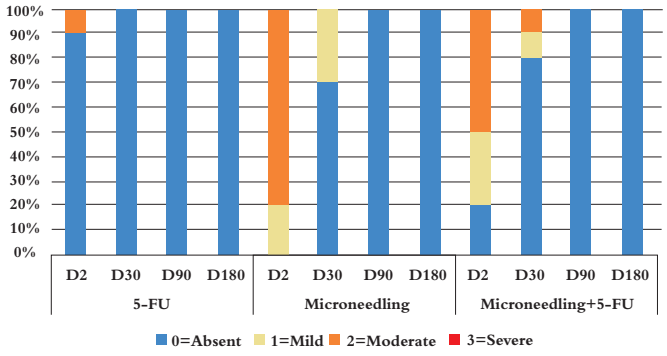
In the group treated with 5-FU, we observed that on day 30, all patients (100%) showed hyperpigmentation, with complete resolution of this adverse effect before the end of the study (day 180). Regarding microneedling alone, only 40% (four buttocks) of the cases showed hyperpigmentation on day 30, absent in the following visits. In patients treated with microneedling+5-FU, 80% (eight buttocks) showed hyperpigmentation on day 30, 50% (five buttocks) on day 90 and 10% (one buttock) maintained this adverse effect until the end of the study (Graph 6).



Graph 3: Percentages of results for patient subjective burning sensation over treatment days



Graph 4: Percentages of results for patient subjective pruritus over treatment days

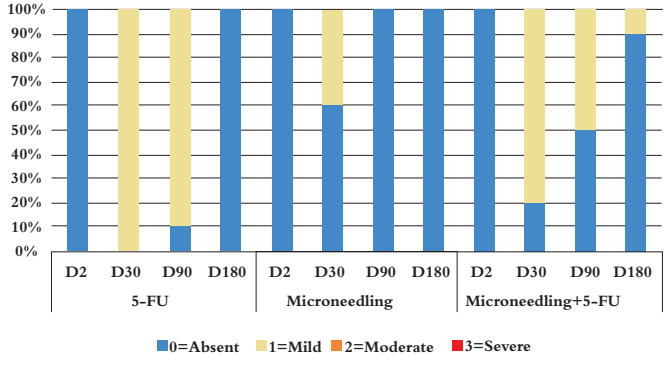


Graph 5: Percentages of results for patient subjective erythema over treatment days

DISCUSSION

In this study, 20% of the buttocks treated with microneedling alone or associated to 5-FU had excellent or very good response. Despite the absence of statistical difference regarding the degree of improvement between the three techniques, it is worth highlighting that in the group of 5-FU alone, no buttock achieved an excellent or very good result. However, most buttocks treated with any one of the modalities achieved, at least, mild improvement of the lesions. The lack of statistical significance can be explained by the sample with reduced number participants or due to the single treatment application.

Nassar *et al* compared microneedling and microdermabrasion with sonophoresis for the treatment of stretch marks on the thighs and legs. In this study, they included 40 patients, [20] Treated with three sessions of microneedling and the remaining with 10 sessions of the other technique. They observed that, with microneedling, six (30%) showed excellent results and eight (40%) very good, against two patients (10%) with excellent response and six (30%) very good with the other technique.[18] In a similar study, Park *et al* treated 16 patients with stretch marks in different locations with three sessions of microneedling without comparing it to other techniques. They observed an excellent improvement in seven (43.8%) patients and minimal to moderate improvement in nine (56.2%).[7] In this protocol, we obtained



Graph 6: Percentages of results for patient hyperpigmentation over treatment days

20% success with microneedling alone or associated to 5-FU with only one session.

In the study by El-Samad *et al*, 60 patients with vitiligo were treated with intralesional 5-FU associated to NB-UVB. As a result, there was increased global repigmentation on the side treated with 5-FU when compared to the one treated with NB-UVB alone, on all parts of the body ($p < 0.001$).[14] The study by Kalil *et al* suggests that the association of one medication or cosmetic formulation with microneedling could enhance the result in 28%.[8] In this study, the group of 5-FU alone demonstrated a mild response in 70% of cases and good in 20%. In the group of microneedling with 5-FU, 10% achieved an excellent response; 10%, very good; and 60%, mild. Despite the difference between the techniques not being statistically significant, we believe that 5-FU associated to microneedling can be more effective.

Regarding patient satisfaction, the three treatments had good evaluations. The techniques of microneedling alone or associated to 5-FU were considered very good and good by 40% and 50% of the participants, respectively. In the group treated with 5-FU alone, we observed that 20% and 60% of patients considered the technique as very good and good, in this sequence. We concluded that, despite not having a statistical difference between the treatments, the level of satisfaction was higher in those patients submitted to the techniques with microneedling. This finding is positively correlated to the degree of improvement obtained with these techniques.

Regarding the subjective parameter of irritation, burning sensation was higher with microneedling and microneedling with 5-FU on day 2 (visit 2) when compared to burning sensation caused by the treatment with 5-FU alone. In the following visits, there was no burning sensation for any of the patients. This initial discomfort is explained by the use of needling, causing trauma to the skin, associated to the effect of burning sensation generated after 5-FU application, as reported in the literature.[6,7,18]

Pruritus from treatments with microneedling on day 2 (visit 2) and day 30 (visit 3) was also slightly worse when compared to the treatment with 5-FU alone. However, there was no statistically significant difference between the treatments. We verified that there are no publications reporting pruritus after these treatments, however, in this study, pruritus was mild and transient in most cases.

The erythema of treatments with needling was much more pronounced when compared to treatment with 5-FU alone on day 2 (visit 2). On day 30, the erythema was still slightly more intense in the treatments with microneedling. In 2013, Lima *et al* described that, after injury caused by microneedles in the skin, vascular ectasia and leakage of red blood cells take place in the dermis. Thus, erythema is explained by the presence of traumas with vascular involvement, being a desired effect in the removal of damaged subepidermal collagen followed by replacement by new collagen and elastin fibers.[6]

In this study, we determined that hyperpigmentation was present in the three treatment groups, however, it was more prevalent in patients treated with 5-FU alone on the visits of days 30 and 90 when compared to the other techniques. We observed that this effect disappeared before the end of this protocol, except for a patient treated with microneedling plus 5-FU, in which the stretch mark maintained the coloration of three tones above the color of the adjacent skin up until the last visit.

In all studies evaluated on the treatment of stretch marks with microneedling alone, we find only the citation of post-inflammatory hyperpigmentation, but transient in nature.[7,18]

The main limitations of this study were the small size of the sample and the restriction to one treatment session, whereas in the literature the final result was assessed after three sessions, as in the studies by Nassar and Park.[7,18]

CONCLUSION

In this study, there was excellent (10%) and very good (10%) clinical improvement in the cases treated with microneedling + 5-FU. Microneedling alone obtained a very good response in 20% of cases, while no patient showed excellent or very good responses with 5-FU alone. However, all techniques showed mild degree of improvement of the lesions.

This way, we verified that the groups treated with microneedling with or without 5-FU obtained excellent and very good results, not observed in those treated with 5-FU alone. These results correlated positively to the degree of patient satisfaction, that was higher among those being treated with needling therapies. However, there was no statistical difference in the two parameters evaluated.

We observed with all three techniques the presence of pain, burning sensation, pruritis and erythema, but predominantly mild and transient in nature. Of the 15 patients treated, residual hyperpigmentation persisted in only one. Thus, we conclude that the therapies are safe and well tolerated.

With this study we noticed that the application of more sessions would probably yield better clinical results. Therefore, we propose new studies comparing the three techniques, with a larger sample, to evaluate if more sessions would result in more expressive results. ●

AKNOWLEDGEMENTS

To Doctor Ada Regina Trindade de Almeida for the support and encouragement given. I would also like to thank the trust of this spectacular teacher. To Doctor Maria Victoria Suarez Restrepo for the valuable guidance offered and to Doctor Liliana Bechelli de Oliveira Torloni, for the availability and for helping me in the execution of this study. To the friends: Jaqueline Guerra, Patrícia de Jesus Resende de Morais and Lelia Barbosa Freire for the invaluable collaboration. To the patients that participated in this project for believing in what was proposed.

REFERENCES

1. Fatemi Naeini F, Behfar S, Abtahi-Naeini B, Keyvan S, Pourazizi M. Promising Option for Treatment of Striae Alba: Fractionated Microneedle Radiofrequency in Combination with Fractional Carbon Dioxide Laser. Dermatol Res Pract. 2016; Mar; 21 (2): 70-76.
2. Bertin C, Lopes-Da Cunha A, Nkengne A, Roure R, Stamatas GN. Striae distensae are characterized by distinct microstructural features as measured by non-invasive methods in vivo. Skin Res Technol. 2014 Feb; 20(1):81-6.
3. Mitts TF, Jimenez F, Hinek A. Skin biopsy analysis reveals predisposition to stretch mark formation. Aesthet Surg J. 2005 Nov-Dec; 25(6):593-600.
4. Cordeiro RCT, Moraes AM. Striae distensae: fisiopatologia. Surg Cosmet Dermatol.2009;1(3):137-140.
5. Crocco EI, Mantovani PA, Volpini BMF. Em busca dos tratamentos para Striae Rubra e Striae Alba: o desafio do dermatologista. Surg Cosmet Dermatol.2012;4(4):332-7.
6. Lima EVA, Lima MA, Takano D. Microagulhamento: estudo experimental e classificação da injúria provocada. Surg Cosmet Dermatol 2013;5(2):1104.
7. Park KY, Kim HK, Kim SE, Kim BJ, Kim MN.Treatment of striae distensae using needling therapy: a pilot study. Dermatol Surg. 2012 Nov;38(11):1823-8.
8. Kalil C, Campos V, Reinehr CPH, Chaves CRPC. Microagulhamento: série de casos associados drug delivery. Surg Cosmet Dermatol 2017;9(1):96-9.
9. Bijlard E, Steltenpool S, Niessen FB. Intralesional 5-Fluorouracil in Keloid Treatment: A Systematic Review. Acta Derm Venereol. 2015 Oct;95(7):778-82
10. Apikian M, Goodman G. Intralesional 5-fluorouracil in the treatment of keloid scars. Australas. J Dermatol 2004;45:140-3
11. Gupta S, Kalra A. Efficacy and safety of intralesional 5-fluorouracil in the treatment of keloids. Dermatology. 2002;204(2):130-2.
12. Metsavaht LD, Garcia CAR. Infiltrações intralesionais de 5-FU no tratamento de queloides, cicatrizes hipertróficas e contraturas. Surg Cosmet Dermatol 2015;7(1):17-24.
13. Gauthier Y, Anbar T, Lepreux S, Cario-André M, Benzekri L. Possible mechanisms by which topical 5-Fluorouracil and dermabrasion could induce pigment spread in vitiligo skin: an experimental study. ISRN Dermatol. 2013 Apr9;2013:852497.
14. Abd El-Samad Z, Shaaban D. Treatment of localized non-segmental vitiligo with intradermal 5-flurouracil injection combined with narrow-band ultraviolet B: a preliminary study. J Dermatolog Treat. 2012 ;23(6):443-8.
15. Fulton JEJ, Rahimi AD, Mansoor S, et al. The treatente of hypopigmentation after skin resurfacing. Dermatol Surg.2004;30:95-101.
16. Arbache S, Godoy C E. Microinfusão de medicamentos na pele através de máquina de tatuagem. Surg Cosmet Dermatol 2013;5(1):704
17. Arbache S, Roth D, Steiner D, Breunig J, Michalany NS, Arbache ST, de Souza LG, Hirata SH. Activation of melanocytes in idiopathic guttate hypomelanosis after 5-fluorouracil infusion using a tattoo machine: Preliminary analysis of a randomized, split-body, single blinded, placebo controlled clinical trial. J Am Acad Dermatol. 2018;78(1):212-215
18. Nassar A, Ghomey S, El Gohary Y, El-Desoky F. Treatment of striae distensae with needling therapy versus microdermabrasion with sonophoresis. J Cosmet Laser Ther. 2016 ;18(6):330-4.

DECLARATION OF PARTICIPATION:

Danielle Claudino de Oliveira Costa | ORCID 0000-0002-3238-6898
Design and planning of the study; preparation and writing of the manuscript; data collection, analysis and interpretation; intellectual participation in propaedeutics and/or therapeutics of the studied cases; critical literature review.

Ada Regina Trindade de Almeida | ORCID 0000-0002-4054-2344
Design and planning of the study; preparation and writing of the manuscript; hands-on participation in mentoring the research; intellectual participation in propaedeutics and/or therapeutics of the studied cases; critical literature review; critical review of the manuscript.

Maria Victoria Suarez Restrepo | ORCID 0000-0002-2614-6011
Statistical analysis; design and planning of the study; preparation and writing of the manuscript; data collection, analysis and interpretation; intellectual participation in propaedeutics and/or therapeutics of the studied cases; hands-on participation in mentoring the research; critical review of the manuscript.

Liliana Bechelli de Oliveira Torloni | ORCID 0000-0002-3876-3148
Data collection, analysis and interpretation; critical review of the manuscript.

Original Articles

Authors:
Thamiris Antonini Marçon[1]
Beatrice Abdalla[1]
Silvia Arroyo Rstom[1]
Carlos D'Apparecida Santos Machado Filho[1]
Francisco Macedo Paschoal[1]

[1] Department of Dermatology, Faculdade de Medicina do ABC - Santo André (SP), Brazil

Correspondence:
Beatrice Martinez Zugaib Abdalla
Av. Lauro Gomes, 2000
Vila Sacadura Cabral
09060-870, Santo André, SP
Brasil
E-mail: bmzabdalla@gmail.com

Received on: 09/12/2018
Approved on: 10/01/2019

Study conducted at the institution: Faculdade de Medicina do ABC - Santo André (SP), Brazil

Financial support: None
Conflict of interests: None

The use of photodynamic therapy with methyl aminolevulinate and daylight for the treatment of actinic keratoses

O uso da terapia fotodinâmica com aminolevulinato de metila e luz do dia para tratamento de queratoses actínicas

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111310

ABSTRACT

Introduction: Actinic keratosis (AK) is a pre-malignant lesion that can progress to squamous cell carcinoma. The diagnosis is through clinical, dermatoscopic and confocal microscopy assessment. Currently, the approach is the treatment of the field cancerization, comprising of clinically visible and subclinical AKs, for which photodynamic therapy (PDT) is a therapeutic option.

Objective: To evaluate improvement of AKs and cancerization field in patients submitted to daylight PDT, with clinical, dermatoscopic and confocal microscopy assessment.

Methods: Ten patients with multiple AKs on the face were selected. Daylight PDT was performed using methyl aminolevulinate and clinical, dermatoscopic and confocal microscopy photographic documentation was performed before and 60 days after the treatment.

Results: Of the nine patients who completed the treatment, 8 (88.8%) showed clinical improvement and reduction in the severity of AK with one treatment. On dermatoscopy, 4 patients (44.4%) showed significant improvement, 3 patients (33.3%) showed partial improvement and 2 patients (22.2%) had no change. On confocal microscopy, 6 (66.6%) patients presented reduction in the severity of the lesion.

Conclusions: Daylight PDT proved to be effective for the treatment of AKs, with high tolerability and efficacy, besides a good safety profile.

Keywords: Dermoscopy; Keratosis, Actinic; Microscopy, Confocal; Photochemotherapy

RESUMO

Introdução*: A queratose actínica (QA) é lesão pré-maligna que pode progredir para carcinoma espinocelular. O diagnóstico é clínico, dermatoscópico e por microscopia confocal. Atualmente, aborda-se o tratamento do campo cancerizável, abrangendo QAs clinicamente visíveis e subclínicas, sendo a terapia fotodinâmica (PDT) uma opção terapêutica.*

Objetivo: *Avaliar melhora das QAs e campo cancerizável em pacientes submetidos a PDT com luz do dia, com análise clínica, dermatoscópica e por microscopia confocal.*

Métodos: *Foram selecionados dez pacientes, com múltiplas QAs na face. Realizada a PDT utilizando luz do dia com aminolevulinato de metila e feita documentação fotográfica clínica, dermatoscópica e por microscopia confocal antes do tratamento e 60 dias após seu início.*

Resultados: *Dos nove pacientes que completaram o tratamento, oito (88,8%) apresentaram melhora clínica e regressão no grau da QA com uma sessão. Na dermatoscopia, quatro pacientes (44,4%) apresentaram melhora significativa, três pacientes (33,3%) apresentaram melhora parcial e dois pacientes (22,2%) tiveram suas lesões estáveis. Na microscopia confocal, seis (66,6%) pacientes tiveram regressão no grau da lesão.*

Conclusões: *A PDT com luz do dia se mostrou eficaz para tratamento de QAs, apresentando alto grau de tolerabilidade e eficácia, além de bom perfil de segurança.*

Palavras-chave: *Ceratose Actínica; Dermoscopia; Fotoquimioterapia; Microscopia Confocal*

INTRODUCTION

Actinic keratosis (AK) is one of the cutaneous lesions that most commonly progresses to squamous cell carcinoma (SCC), being a result of excessive exposure to ultraviolet light.[1-3] These lesions can undergo spontaneous regression, clinical stability or progression to SCC in a percentage ranging from 0.1 to 20% of cases in up to ten years.[4] Its diagnosis is clinical, based on the presence of papules or erythematous plaques with white scales on photoexposed areas (face, scalp, chest and upper limbs).[5] On dermoscopy, white scales and yellow follicular openings on an erythematous base can be seen, giving the aspect of pseudo-network or 'strawberry'.[6] On confocal microscopy in vivo, an instrument of extensive applicability in the dermatological practice, that allows for the visualization on a cellular level with an almost histological resolution of cell and tissue features with a safe, noninvasive and real-time method,[7,8] actinic keratoses can be seen by the hyperkeratosis (presence of white shiny scales on examination), irregular or atypical honeycomb pattern on the horny and granular layers of the epidermis and the presence of atypical keratinocytes.[6]

Treatment of actinic keratoses is important because it involves the prevention of progression of a pre-malignant lesion to squamous cell carcinoma, and many modalities can be used: cryotherapy with liquid nitrogen, surgical excision, curettage, topical medications (5-fluorouracil, trichloroacetic acid, imiquimod, ingenol mebutate and photodynamic therapy.[2,4]

Lately, the treatment of the cancerization field has been approached, defined as the presence of multiple actinic keratoses on photoexposed areas, associated to the presence of dysplastic keratinocytes on the adjacent skin (interlesional). Thus, treatment of these areas involves both clinically visible actinic keratosis and subclinical lesions.[5]

Photodynamic therapy (PDT) is a treatment where selective destruction of the target tissue takes place through a photochemical reaction using a photosensitizing substance, light and oxygen.[9-11] This therapeutic modality can be used in the conventional form or with day light. In conventional PDT, the agents applied on the skin are later activated by specific light sources (broad spectrum lights, diode and laser lights) and are mainly employed for the treatment of actinic keratosis, low-risk basal cell carcinomas and Bowen's disease, with fast recovery and great cosmetic result.[9,10] Daylight PDT is used for the treatment of grade I and II actinic keratoses, besides cancerization field. The substance applied is methyl aminolevulinate, that undergoes continuous metabolization into photoactive protoporphyrins, particularly protoporphyrin IX (PpIX), leading to an increased sensitivity to light only on the damaged cells.[10] This way, with exposure to light, the molecules of activated porphyrins react with oxygen forming highly toxic reactive oxygen species (ROS), culminating in cell death.[10,11]

The objective of this study was to evaluate the improvement on actinic keratoses and cancerization field in patients submitted to daylight photodynamic therapy with methyl aminolevulinate through clinical, dermoscopic and confocal microscopy analysis.

METHODS

From April 2016 to February 2017, 10 patients from the Outpatient Clinic of Dermatology from the Faculdade de Medicina do ABC, Santo André (SP), Fitzpatrick phototypes between I and III, older than 40 years, with multiple actinic keratoses (mostly grade I and II) on the face were selected; these patients signed the consent form and the study took place according to the ethical principles emanated from the Declaration of Helsinki. One lesion of actinic keratosis was selected on the face of each patient with clinical (Nikon DX AF-S Nikkor 18-105mm), dermoscopic (Dermoscope 3Gen DermLite®, United States) and confocal microscopy (VivaScope 3000 Caliber ID®, United States) photographic record before treatment and after 60 days.

Treatment consisted in cleansing the skin to be treated with aqueous chlorhexidine, superficial curettage of the scales of actinic keratoses, application of sunscreen without physical filters (Actinica® FPS 50, Galderma) and subsequent application of a thin layer of 16% methyl aminolevulinate (Metvix®, Galderma - France) all over the face (as guided by the product information), followed by continuous sun exposure for two hours, followed by removal of the product with plain washing of the skin, and instruction to spend the rest of the day indoors, without sun exposure.

Sixty days after performing daylight PDT, the patients were re-evaluated and new photographic documentation was performed. One patient was excluded from the study because she did not attend the re-evaluation after 60 days as previously agreed upon.

Response to treatment was graded from 1 to 4 (1: significant improvement; 2: partial improvement; 3: stable lesion; 4: worsening of the lesion) on three parameters evaluated: clinical aspect, dermoscopy and confocal microscopy.

RESULTS

Of the nine patients that completed the proposed treatment, four (44.4%) showed significant clinical improvement and four (44.4%) showed partial improvement. Therefore, eight of the nine patients (88.8%) improved the clinical aspect with regression of the grade of the actinic keratosis with one daylight PDT session.

Regarding dermoscopy, four patients (44.4%) showed significant improvement, being considered the improvement of the hyperkeratosis (scales) and the 'strawberry' pattern, and three patients (33.3%) showed partial improvement; this way, seven out of the nine patients (77.7%) showed improvement on the dermoscopic features. The two patients (22.2%) with stable lesion were graded like this, because even though they had initial improvement of the hyperkeratosis, there was early recurrence, determining a stable lesion.

Regarding confocal microscopy, four patients (44.4%) showed significant improvement, two patients (22.2%) showed partial improvement, so 66.6% of patients had regression on the grade of the lesion, evaluated by the improvement on the atypical honeycomb pattern, the hyperkeratosis and cell atypia.

These results, as well as the characteristics of the patients and the area of the lesions, are represented on table 1 and in figure 1. It is important to highlight that, besides the improvement on actinic keratoses evaluated clinically and dermoscopically, and by Confocal microscopy, all nine patients showed improvement on the global quality of the facial skin, both in lightening of hyperpigmentation and in smoothening of fine wrinkles and skin laxity, corroborating the findings of other studies that indicate photodynamic therapy as having an effect in the improvement of cutaneous ageing (Figure 2).

During the procedure, all patients classified the treatment as painless, attributing zero (ranging from zero to ten) to pain during sun exposure. The patients developed erythema after treatment, that ranged from 1 to 4 days, and 2 patients had edema for 2 days.

DISCUSSION

Actinic keratoses represent the initial stage in the development of a squamous cell carcinoma and represent important markers for patients at risk of developing skin cancer.[6] Multiple treatments are proposed aiming at regression and non-progression of these lesions to SCC, besides improvement in the cancerization field such as cryotherapy with liquid nitrogen, 5-Fluoruracil, Imiquimod and Ingenol Mebutate.[4,5] Photody-

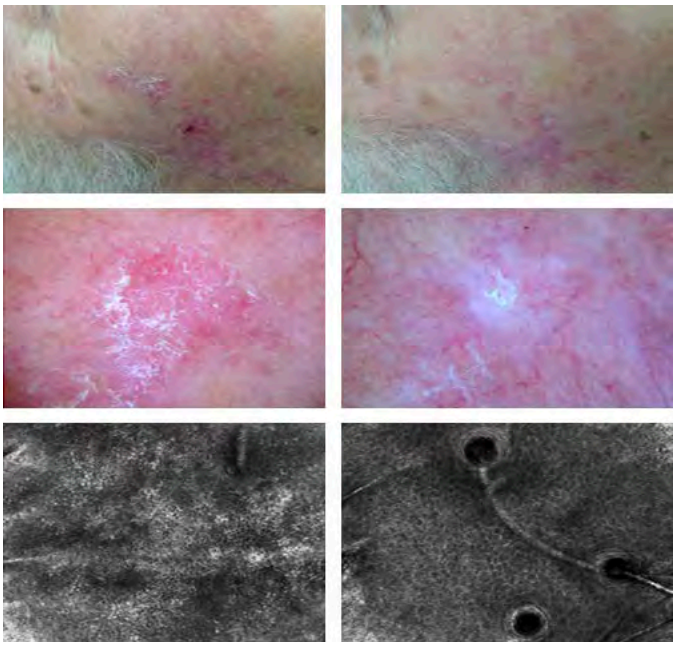


Figure 1: Actinic keratosis of patient 7: before (left) and after (right) treatment with one session of daylight photodynamic therapy; images demonstrate significant improvement in clinical aspect, dermoscopy (reduction of scales and erythema) and on confocal microscopy (improvement of the honeycomb pattern, which became more regular and typical)

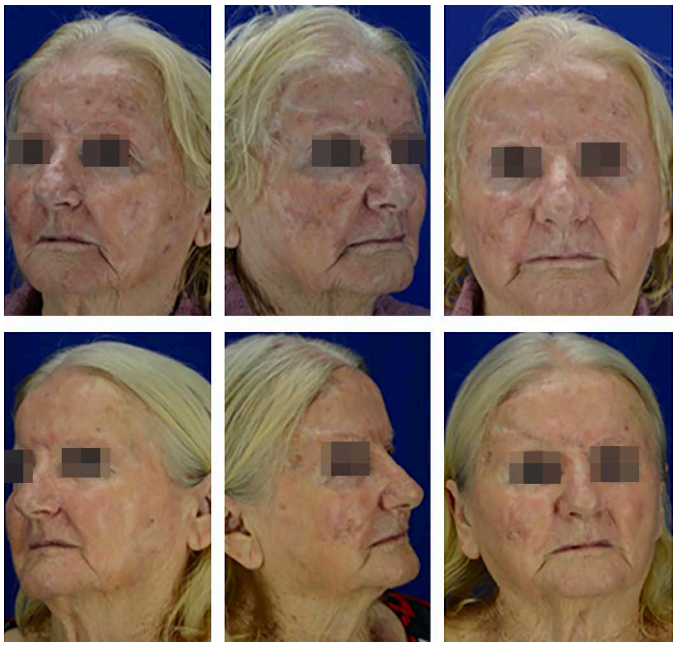


Figure 2: Improvement on the overall quality of the skin and laxity of the skin: before (top photos) and after (bottom photos) treatment with one session of daylight photodynamic therapy

Table 1: Profile of the participants and response shown after one session of daylight photodynamic therapy

Patient	Sex/Age	Area of the lesion	Clinical response	Dermoscopy response	Response on confocal microscopy
1	M/72	L Malar	1	1	1
2	W/44	R Malar	2	2	2
3	W/	L Eyebrow	2	2	3
4	W/	L Mandibular	1	1	1
5	M/67	L Malar	2	3	3
6	W/81	R Malar	3	3	3
7	W/80	R Pre-auricular	1	1	1
8	W/	R Malar	1	1	1
9	W/74	R Malar	2	2	2

L: LEFT; R: RIGHT

1: SIGNIFICANT IMPROVEMENT; 2: PARTIAL IMPROVEMENT; 3: STABLE; 4: WORSE

namic therapy, both conventional and daylight, has been widely used for the treatment of actinic keratoses and cancerization field, demonstrating similar efficacy between both modalities confirmed by randomized, multicentric studies like those by Wiegell,[13,15,16,18] Rubel[3] and Lacour *et al*.[17] This study corroborates the efficacy of daylight photodynamic therapy for the treatment of AKs, since there was improvement of the lesions, with regression on their grade in most patients.

We also highlight the importance of the evaluation of these lesions with the aid of complementary diagnostic tools, such as dermoscopy and confocal microscopy. There are few studies using these methods to compare pre- and post-treatment lesions. Jafari *et al* studied 40 AKs with daylight PDT by clinical response and confocal microscopy and concluded that 80% of the lesions (n = 32) showed complete regression, 17.5% (n = 7) showed partial response and only one lesion remained unchanged; with confocal microscopy, they concluded that 57.5% (n = 23) of the lesions did not show cellular atypia and 40% (n = 16) showed little atypia, when compared to the pre-treatment assessment; they also observed improvement of the honeycomb pattern hyperkeratosis, which became more regular and typical.

Most patients of this study showed clinical (88.8%), dermoscopic (77.7%) and confocal microscopy (66.6%) improvement; however, we cannot state that there was total regression of the lesions, a result that is not in keeping with the previous studies mentioned.

We also highlight that all patients were satisfied with the treatment, considered it painless and showed improvement on the overall quality of the facial skin, with smoother fine wrinkles, telangiectasias and erythema, results already previously seen when treating AKs and cancerization field with daylight PDT.[19]

This study has limitations such as small sample of patients (n = 9), lack of a control group and subjectivity in the exact qualification of diagnostic improvement, for example, for determining the grade of cellular atypia with confocal microscopy; however, the efficacy of the proposed treatment is certain.

CONCLUSION

Daylight photodynamic therapy proved to be effective for the treatment of actinic keratoses on the face, with improvement seen clinically, dermoscopically and on confocal microscopy. It is a treatment that represents an excellent option for the treatment of these lesions since it is well-tolerated by patients, highly effective, and has a good safety profile. ●

ACKNOWLEDGEMENTS

To the mentors, Prof. Francisco Macedo Paschoal and Carlos D'Apparecida S. Machado Filho, and to the collaborators in the article.

REFERENCES

1. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol. 2000;42(1Pt 2):4-7.
2. Wiegell SR. Daylight photodynamic therapy for actinic keratosis: an international consensus: International Society for Photodynamic Therapy in Dermatology. J Eur Acad Dermatol Venereol. 2012;26(6):673-679.
3. Rubel DM. Daylight PDT with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional PDT in actinic keratosis treatment: a randomised controlled trial. Br J Dermatol. 2014;171(5):1164-1171.
4. Costa C, Scalvenzi M, Ayala F, Fabbrocini G, Monfrecola G. How to treat actinic keratosis? An update. J Dermatol Case Rep. 2015;9(2):29-35.
5. Stockfleth E, Ortonne J-P, Alomar A. Actinic keratosis and field cancerisation. Eur J Dermatol 2011; 21: 1-12.
6. Zalaudek I, Piana S, Moscarella E, Longo C, Zendri E, Castagnetti F, et al . Morphologic grading and treatment of facial actinic keratosis. Clin Dermatol. 2014;32(1):80-7.
7. Selkin B, Rajadhyaksha M, Gonzalez S, Langley RG. In vivo confocal microscopy in dermatology. Dermatol Clin. 2001;19(2):369-77.
8. Aghassi D, Anderson R, Gonzalez S. Confocal laser microscopic imaging of actinic keratoses in vivo: a preliminary report. J Am Acad Dermatol. 2000;43(1 Pt 1):42-8.
9. Issa MCA, Manela-Azulay M. Terapia fotodinâmica: revisão da literatura e documentação iconográfica. An Bras Dermatol. 2010;85(4):501-11.
10. Torezan L, Niwa ABM, Festa Neto C. Photodynamic therapy in dermatology: basic principles. An Bras Dermatol. 2009;84(5):445-5.
11. Rubel DM, Spelman L, Murrell DF, See JA, Hewitt D, Foley P, et al. Daylight photodynamic therapy with methyl aminolevulinate cream as a con-venient, similarly effective, nearly painless alternative to conventional photodynamic therapy in actinic keratosis treatment: a randomized controlled trial. Br J Dermatol. 2014;171(5):1164-71.
12. Braathen LR, Szeimies RM, Basset-Seguin N, Bissonnette R, Foley P, Pariser D, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. J Am Acad Dermatol. 2007;56(1):125-43.
13. Wiegell SR, Fabricius S, Stender IM, Berne B, Kroon S, Andersen BL, et al. A randomized, multicentre study of directed daylight exposure times of 1½ vs. 2½ h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp. Br J Dermatol. 2011;164(5):1083-90.
14. Jafari SMS, Timchik T, Hunger RE. In vivo confocal microscopy efficacy assessment of daylight photodynamic therapy in actinic keratosis patients. Br J Dermatol. 2016;175(2):375-381.
15. Wiegell SR, Fabricius S, Gniadecka M, Stender IM, Berne B, Kroon S, et al. Daylight-mediated photodynamic therapy of moderate to thick actinic keratoses of the face and scalp: a randomized multicentre study. Br J Dermatol. 2012;166(6):1327-32.
16. Wiegell SR, Haedersdal M, Philipsen PA, Enk CD, Wulf HC. Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study. Br J Dermatol. 2008;158(4):740-746.
17. Lacour JP, Ulrich C, Gilaberte Y, Von Felbert V, Basset-Seguin N, Dreno B, et al. Daylight photodynamic therapy with methyl aminolevulinate cream is effective and nearly painless in treating actinic keratoses: a randomised, investigator-blinded, controlled, phase III study throughout Europe. J Eur Acad Dermatol Venereol. 2015;29(12):2342-8.
18. Wiegell SR, Haedersdal M, Eriksen P, Wulf HC. Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial. Br J Dermatol. 2009;160(6):1308-14.
19. Morton CA, McKenna KE, Rhodes LE, British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update. Br J Dermatol. 2008;159(6):1246-66.

DECLARATION OF PARTICIPATION:

Thamiris Antonini Marçon | ORCID 0000-0002-7568-5230
Statistical analysis, approval of the final version of the original, design and planning of the study, preparation and writing of the manuscript, data collection, analysis and interpretation, active participation on mentoring the research, intellectual participation in propaedeutics and/or therapeutics in the cases studied, critical review of the literature, critical review of the original.

Beatrice Abdalla | ORCID 0000-0003-4586-1915
Preparation and writing of the original, critical review of the original.

Silvia Arroyo Rstom | ORCID 0000-0001-89754148
Approval of the final version of the original, design and planning of the study, critical review of the original.

Carlos D'Apparecida Santos Machado Filho | ORCID 0000-0003-4362-1563
Approval of the final version of the original, critical review of the original.

Francisco Macedo Paschoal | ORCID 0000-0002-6264-1538
Design and planning of the study, active participation on mentoring the research, critical review of the original.

Growth factors and healing: experience in a Dermatology service

Fatores de crescimento e cicatrização: experiência em um serviço de Dermatologia

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111313

ABSTRACT

Introduction: Healing is a phenomenon that occurs after tissue injury and involves complex cellular and molecular mechanisms. Growth factors seem to be an effective and safe complement for the treatment of wounds.

Objective: To evaluate wound healing after electrocoagulation, comparing the vehicle in isolation and its association with epidermal growth factor.

Methods: Double-blind clinical trial in a Dermatology service between 2016 and 2018. Patients of both genders, older than 18 years of age, submitted to electrocoagulation of two lesions and subsequent application of the vehicle (*cold cream*) on one and epidermal growth factor in *cold cream* on the other were included. Evaluations after 7, 14 and 28 days, analysed erythema, edema, crusting, discharge and healing. Analyzed: edema, edema, crusting, discharge and healing. The binomial test was used for two ratios and Fisher's exact test was used for dichotomic data.

Results: Variable results were found regarding erythema, edema, crusting and discharge, sometimes favoring the vehicle, sometimes the growth factor, however with no statistical significance. Regarding healing, epithelialization was quicker with epidermal growth factor ($p<0.05$).

Conclusions: This study evaluated the impact of epidermal growth factor in the healing process, and its results reinforce scarce data of the current literature and are a foundation for future studies.

Keywords: Epidermal growth factor; Evaluation; Wound healing

RESUMO

Introdução: *A cicatrização é um fenômeno que ocorre após lesão tecidual e envolve mecanismos celulares e moleculares complexos. Os fatores de crescimento parecem ser um complemento eficaz e seguro no tratamento das feridas.*

Objetivo: *Avaliar a cicatrização de feridas após eletrocoagulação, comparando-se o veículo isolado à sua associação com o fator de crescimento epidérmico.*

Métodos: *Ensaio clínico duplo-cego em Serviço de Dermatologia entre 2016 e 2018. Incluídos pacientes de ambos os sexos, acima de 18 anos, submetidos à eletrocoagulação de duas lesões e posterior aplicação de veículo (cold cream) em uma e fator de crescimento epidermico em cold cream na outra. Avaliações com sete, 14 e 28 dias, analisaram: eritema, edema, crosta, secreção e cicatrização. Utilizou-se o teste binomial para duas proporções e o teste exato de Fisher para dados dicotômicos.*

Resultados: *Em relação a eritema, edema, crosta e secreção foram encontrados resultados variáveis, ora favorecendo o veículo, ora o fator de crescimento, porém sem significância estatística. Quanto à cicatrização, a epitelização mostrou-se mais rápida com fator de crescimento epidermico ($p<0,05$).*

Conclusões: *Os resultados deste estudo, que avaliou o impacto do fator de crescimento epidérmico no processo de cicatrização, corroboram os dados da escassa literatura atual e servem de base para estudos futuros.*

Palavras-Chave: *Avaliação de medicamentos; Cicatrização; Fator de crescimento epidérmico*

Original Articles

Authors:
Felipe Siqueira Ramos[1]
Elisangela Manfredini Andraus de Lima[1]
Flávia Regina Ferreira[1]
Samuel Henrique Mandelbaum[1]

[1] Service of Dermatology, Hospital Universitário de Taubaté, Universidade de Taubaté – Taubaté (SP), Brazil.

Correspondence:
Felipe Siqueira Ramos
Avenida Granadeiro Guimarães, 270
Centro
12020-130, Taubaté, SP
E-mail: siqueira_ramos@hotmail.com

Received on: 10/12/2018
Approved on: 22/01/2019

Study conducted at Taubaté University Hospital, Universidade de Taubaté - Taubaté (SP), Brazil.

Financial support: The products used, Epifactor® e *cold cream*, were given by the company Infinity Pharma, Campinas (SP).
Conflict of interests: None

INTRODUCTION

Healing is a phenomenon that occurs after tissue injury of any nature and involves complex cellular and molecular mechanisms. Inflammation, proliferation, angiogenesis, reepithelization, tissue regeneration and remodeling are part of this biological process.[1] Thermal burns (accidental or intentional) generate areas of necrosis that extend beyond the wound, even causing obstruction of blood and lymphatic vessels.[2]

The process of tissue repair is modulated by growth factors, that are produced by epidermal and epithelial cells, such as macrophages, fibroblasts and keratinocytes. Growth factors are biologically active molecules and act directly from within the cell, regulating the cell cycle.[3] However, the availability of these growth factors can be insufficient in the bed of the wound resulting from burns due to their excessive degradation or reduced production. Therefore, treatment with growth factors seems to be an effective and safe complement to the treatment of wounds.[4,5] The objective of this study was to evaluate wound healing after electrocoagulation comparing the vehicle alone (cold cream) to its association with epidermal growth factor.

METHODS

This is a comparative, double-blind clinical trial, conducted at a Service of Dermatology between June 2016 and July 2018. Patients from both genders and older than 18 years of age were included, with two lesions similar in nature and size, on the same body area. Both lesions were submitted to electrocoagulation, with subsequent daily application of the vehicle (cold cream) on one and 5% epidermal growth factor in cold cream (Epifactor®) on the other, for 28 days. Evaluations were performed after 7, 14 and 28 days, and the wounds photographed according to the standardization. These photos were then evaluated by an independent researcher (dermatologist). The variables analyzed were: erythema, edema the use of the vehicle alone. However, on the 28th day, both groups had a coinciding end result for this variable. (presence or absence and intensity), crust, discharge (presence or absence) and healing (crust, ulceration and epithelization). Tables were made. For the comparison between two independent samples, the binomial test was used for two of significance adopted was alpha = 5%, and the statistical program used was *BioEstat* 5.0. The study was approved by the Committee ratios and Fisher's exact test for dichotomic data. The level of Ethics in Research of the institution under the number 1.861.616.

RESULTS

Thirteen patients were included (seven men and six women), with minimum and maximum ages of 36 and 86 years, respectively.

Table 1 demonstrates the progression of erythema along the 28 days. After 14 days, there were similar percentages between the two groups for this variable, predominating mild erythema. In table 2, we can evaluate data regarding edema. There was an apparent lower initial edema (7th and 14th day) with regarding the variable 'crust formation', data can be seen on table 3. Most wounds (in both groups) showed crust after seven days. The elimination of the crust was faster with the use of the vehicle alone (69.23% of the lesions had no crust on the 14th day).

Table 4 illustrates the variable 'discharge'. In it, we can observe a faster resolution of the discharge in the wounds where Epifactor® was used (100% on the 14th day).

Regarding healing, only 7.69% of the wounds (from both groups) had ulceration on the 7th day (Table 5). The epithelization occurred faster in the wounds where Epifactor® was used (46.15% versus 0% - 14th day), $p<0.05$.

Figure 1 illustrates epithelization of the wound treated with Epifactor® and with vehicle on the 14th day.

DISCUSSION

This original study, evaluating the impact of epidermal growth factor in the healing process, supports the literature

Table 1: Erythema regarding its intensity and the time of evaluation in percentage

Evaluation	7 days		14 days		28 days	
Erythema	EP	CC	EP	CC	EP	CC
	%	%	%	%	%	%
Mild	38.46	46.15	76.92	69.23	69.23	69.23
Moderate	46.15	46.15	23.08	30.77	23.08	23.08
Intense	15.38	7.69	0	0	0	0
Absent	0	0	0	0	7.69	7.69

EP: Epifactor®; CC: Cold cream

Table 2: Edema regarding its intensity and time of evaluation in percentage

Evaluation	7 days		14 days		28 days	
Edema	EP	CC	EP	CC	EP	CC
	%	%	%	%	%	%
Mild	15.38	23.08	15.38	69.23	69.23	69.23
Moderate	53.85	38.46	38.46	30.77	23.08	23.08
Intense	15.38	15.38	0	0	0	0
Absent	15.38	23.08	0	0	7.69	7.69

EP: Epifactor®; CC: Cold cream

Table 3: Crust regarding the presence or absence and time of evaluation in percentage

Evaluation	7 days		14 days		28 days	
Crust	EP	CC	EP	CC	EP	CC
	%	%	%	%	%	%
Absent	15.38	30.77	46.15	69.23	84.62	92.31
Present	84.62	69.23	53.85	30.77	15.38	7.69

EP: Epifactor®; CC: Cold cream

Table 4: Discharge regarding presence or absence and time of evaluation in percentage

Evaluation	7 days		14 days		28 days	
Discharge	EP	CC	EP	CC	EP	CC
	%	%	%	%	%	%
Absent	61.54	61.54	100	84.62	100	100
Present	38.46	38.46	0	15.38	0	0

EP: Epifactor®; CC: Cold cream

Table 5: Healing – Crust, ulceration, epithelization – at the time of evaluation in percentage

Evaluation	7 days		14 days		28 days	
Healing	EP	CC	EP	CC	EP	CC
	%	%	%	%	%	%
Crust	84.62	69.23	53.85	30.77	15.38	15.38
Ulcerated	7.69	7.69	0	69.23	0	0
Epithelialized	7.69	23.08	46.15	0	84.62	84.62

EP: Epifactor®; CC: Cold cream

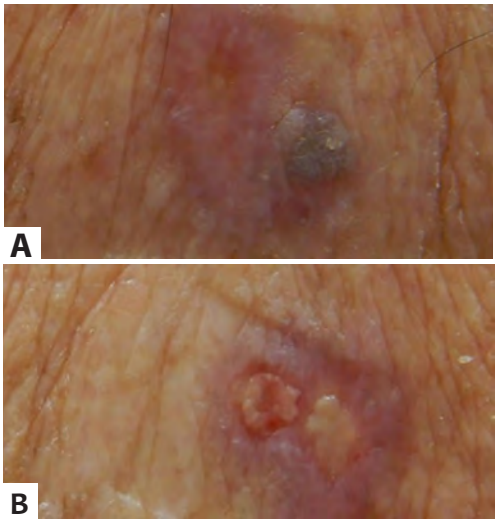


Figure 1: Epithelization.
A – Wound treated with Epifactor®;
B – Wound treated with cold cream (still ulcerated/ fibrine) – 14th day

where studies on this subject are still scarce, what made difficult the discussion of the results found. Regarding the variables erythema, edema, crust and discharge, there was a mild predominance of a better result sometimes for one group, other times for the other, however, with no statistical significance. Healing (epithelization) was faster in the group using epidermal growth factor, supporting the findings by Zhang *et al*, who demonstrated that the topical use of growth factors significantly reduced healing time for partial thickness burn wounds.[4] Limitation: Factors not taken into account in this study, such as gender, age, site, comorbidities, could have interfered with our findings.

CONCLUSION

This study allowed for the evaluation of the healing of wounds after electrocoagulation, comparing the vehicle alone to its association with epidermal growth factor and concluded that the topical use of epidermal growth factor accelerated wound epithelialization, significantly reducing healing time. ●

ACKNOWLEDGEMENTS

To all staff of the Service of Dermatology at University Hospital of Taubaté and to Prof. Dr. Luiz Carlos Laureano da Rosa for the help with the statistical analysis of this study.

REFERENCES

1. Velnar T, Bailey T, Smrkolj V. The Wound Healing Process: an Overview of the Cellular and Molecular Mechanisms. J Int Med Res. 2009;37(5):1528-42.
2. Lee JH, Bae IH, Choi JK, Park JW. Evaluation of a Highly Skin Permeable Low-Molecular-Weight Protamine Conjugated Epidermal Growth Factor for Novel Burn Wound Healing Therapy. J Pharm Sci. 2013;102(11):4109-20.
3. Vieira ACQM, Medeiros LA, Palácio SB, Lyra MAM, Alves LDS, Rolim LA, et al. Fatores de crescimento: uma nova abordagem cosmecêutica para o cuidado antienvelhecimento. Rev Bras Farm. 2011;92(3):80-9.
4. Zhang Y, Wang T, He J, Dong J. Growth factor therapy in patients with partial-thickness burns: a systematic review and meta-analysis. Int Wound J. 2016;13(3):354-66.
5. Marchese C, Chedid M, Dirsc OR, Csaky KG, Santanelli F, Latini C, et al. Modulation of Keratinocyte Growth Factor and its Receptor in Reepithelializing Human Skin. J Exp Med. 1995;182(5):1369-76.

DECLARATION OF PARTICIPATION:

Felipe Siqueira Ramos | ORCID 0000-0002-3109-4359
Statistical analysis, approval of the final version of the manuscript, design and planning of the study, preparation and writing of the manuscript, data collection, analysis and interpretation, active participation in mentoring the research, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the literature, critical review of the manuscript.

Elisangela Manfredini Andraus De Lima | ORCID 0000-0002-2390-0410
Approval of the final version of the manuscript, design and planning of the study, preparation and writing of the manuscript, data collection, analysis and interpretation, active participation in mentoring the research, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the manuscript.

Flávia Regina Ferreira | ORCID 0000-0001-5679-4282
Approval of the final version of the manuscript, design and planning of the study, data collection, analysis and interpretation, active participation in mentoring the research, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the literature, critical review of the manuscript.

Samuel Henrique Mandelbaum | ORCID 0000-0002-4631-4828
Approval of the final version of the manuscript, design and planning of the study.

Botulinum toxin for the treatment of facial hidrocystomas

Toxina botulínica para o tratamento de hidrocistomas faciais

DOI: http://dx.doi.org/10.5935/scd1984-8773.201911101

ABSTRACT

Introduction: Hidrocystomas are skin-colored or translucent cysts, single or multiple, appearing on the face. They originate in the eccrine or apocrine sweat gland and are sometimes disfiguring. They can be treated by surgery, electrodessication, or by caustics, but are usually recurrent and the treatments can leave scars or dyschromia. Botulinum toxin A (BoNT-A) has been suggested as therapy in few cases in the literature.

Objective: To analyze the effects of BoNT-A in cases of facial hidrocystomas.

Methods: Retrospective observational study of case series. Patients with facial hidrocystomas treated with BoNT-A at the Cosmiatry Outpatient Dermatology Clinic of the Hospital do Servidor Público Municipal de São Paulo, were evaluated.

Results: Of the 13 patients evaluated, 5 were included, the largest case series described so far. Of these, all lesions treated showed clinical improvement during the period evaluated. Four patients showed partial regression and one, total regression of the lesions.

Conclusion: In this series of cases, BoNT-A showed positive and long-lasting results in the treatment of facial hidrocytsomas, with no adverse effects.

Keywords: Botulinum toxins; Hidrocystoma; Therapeutics

RESUMO

Introdução: *Hidrocistomas são cistos cor da pele ou translúcidos, únicos ou múltiplos, que aparecem na face. Têm origem na glândula sudorípara écrina ou apócrina e, às vezes, são desfigurantes. Podem ser tratados com cirurgia, eletrodissecção ou cáusticos, mas costumam ser recidivantes e os tratamentos podem deixar cicatrizes ou discromias. A toxina botulínica A (BoNT-A) foi sugerida como terapia em poucos casos na literatura.*

Objetivo: *Analisar os efeitos da toxina botulínica em casos de hidrocistoma da face.*

Métodos: *Estudo observacional retrospectivo de série de casos. Foram avaliados pacientes portadores de hidrocistoma na face, tratados com BoNT-A.*

Resultados: *De 13 pacientes avaliados, cinco foram incluídos, a maior casuística descrita até o momento. Destes, todas as lesões tratadas apresentaram melhora clínica durante o período avaliado. Quatro pacientes mostraram regressão parcial e um, regressão total das lesões.*

Conclusões: *Nesta série de casos, a BoNT-A mostrou resultados positivos e duradouros no tratamento de hidrocistomas faciais, sem efeitos adversos.*

Palavras-chave: *Hidrocistoma; Terapêutica; Toxinas botulínicas*

Original Articles

Authors:
Ada Regina Trindade de Almeida[1]
Jaqueline Guerra[1]
Marcelo Margarido Bellini[1]
Alessandra Ribeiro Romiti[1]
Maria Victoria Súarez Restrepo[1]

[1] Cosmiatry, Outpatient Department of Dermatology, Hospital do Servidor Público Municipal de São Paulo (HSPM-SP) - São Paulo (SP), Brazil

Correspondence:
Dra. Ada Trindade de Almeida
Rua Castro Alves 60
Aclimação
01532-000, São Paulo, SP
Brasil
E-mail: artrindal@uol.com.br

Received on: 20/02/2019
Approved on: 15/03/2019

Study conducted at the Outpatient Department of Dermatology, Hospital do Servidor Público Municipal de São Paulo (HSPM-SP) - São Paulo (SP), Brazil

Financial support: None.
Conflict of interests: None.

INTRODUCTION

Hidrocystomas are translucid or skin-colored cystic lesions, common on the face, particularly around the eyes. They arise from sweat glands, and can be eccrine or apocrine in origin.[1] They are benign, single or multiple, relatively common and more frequent in middle-aged women.[2]

The cause for the appearance is still unclear. Occlusion or blockage of the sweat duct, resulting in sweat retention and consequent dilation of the cystic duct could be one of the possible causes.[2,3] Some authors suggest that hot and humid environments could increase sweat production and act as aggravating factors.[4,5]

Clinically, they appear as one or more lesions of various sizes on the cephalic segment, preferentially on the forehead, malar and palpebral regions, being the external aspect of the lower eyelid the most common site.[6]

On histology, two different types can be seen: apocrine (or Moll's gland cyst) and eccrine, however, clinical differentiation is rarely made, except by the fact that Moll's gland cyst is solitary and preferentially located near the eyelashes and the tear drainage duct and eccrine hidrocystoma is located on the eyelid skin and can be single or multiple.[7] They can still be associated to ectodermal dysplasia syndromes such as Schopf-Schulz-Passarge and Gorlin-Goltz.[6-9]

In the literature, multiple treatments are mentioned such as surgical excision, simple drainage with a needle, caustics as trichloroacetic acid or phenol, carbon dioxide laser and electrodessication.[10] Due to the recurrent nature of the lesions, the risk of unsightly scars and/or dyspigmentation with surgical or ablative procedures is high.

Eccrine sweat glands are innervated by postganglionic sympathetic nerve fibers and regulated by mediators such as acetylcholine, pilocarpine and adrenaline, whereas apocrine glands are mediated by adrenaline, noradrenaline and methacholine.[11] All these mediators can be blocked by botulinum toxin. For this reason, the neuromodulator arose as a therapeutic option, having the advantages of being non-invasive, not presenting risks for residual scarring or dyspigmentation.

BoNT-A is still little used for hidrocystomas as a therapeutic option. The application technique consists in the emptying of the cyst content of the lesion, immediately before the local injection of the drug, with the goal of blocking the stimulus to the production of sweat by sweat glands.[12,13] The dose injected into each lesion is still not standardized and the duration of the effect produced by the toxin is still unclear.

The procedure is simple, well tolerated, with good course after the procedure, and has no risk of scarring.[13] Pain is a transient adverse effect, usually present only during the injection. Headaches, nausea, palpebral ptosis and facial asymmetry are uncommon adverse effects.[2]

The objective of this study is to retrospectively analyze the efficacy and safety of cases of facial hidrocystomas treated with BoNT-A.

METHODS

Retrospective observational study of case series. Patients with facial hidrocystomas were selected from the Sector of Cosmiatry of the Outpatient Department of Dermatology of the Hospital do Servidor Público Municipal, treated with botulinum toxin between January 2014 and December 2015.

Inclusion criteria: Patients from both genders, between 18 and 80 years of age, with at least one hidrocystoma on the face treated with BoNT-A and with clinical and photographic follow-up on the day of the application of the neuromodulator (D0) and 14 (D14), 30 (D30), and between 90 and 120 days (D90 and D120) after the procedure.

Variables analyzed: Demographic data (age and gender of the patient), location and number of lesions (single or multiple), dose (per lesion and total), number of sessions performed and efficacy of the therapy applied. The evaluation of the clinical response to the treatment was performed by an observer not involved in the treatment, through photographic records as follows:

Scale of clinical evaluation:

Complete regression of the lesions; disappearance of the lesions;

Partial regression of the lesions: reduction in the size of the lesions and/or the number of lesions;

No response: unchanged lesions.

Adverse events: the identification of adverse events was performed through data obtained by reviewing the medical records. **Statistical analysis:** Because it is a retrospective observational study, statistical analysis was performed through the description of the findings reported in the medical records.

RESULTS

Thirteen individuals with hidrocystomas on the face treated with BoNT-A were selected in this study. Of these, only five fulfilled the inclusion criteria. The age ranged between 45 and 73 years, the mean being 57.8 years. Four cases were in females (80%) and the phototype ranged from I to VI, with the latter being the most common (40% of the sample). Data on family history of facial hidrocystomas were not found in the medical records analyzed. Most cases (60%) presented a single lesion, and the most common location was on the lateral aspect of the lower eyelid, followed by ocular epicanthus. Histologic differentiation between eccrine and apocrine hidrocystomas was not made.

Botulinum toxin A was reconstituted with 2ml of saline for each vial with 100U. the total dose used in each patient ranged from 5U to 33U, two patients (2 and 4) were treated in only one session, while in three (1, 3 and 5) the second session took place between 15 to 30 days after the first (Table 1).

At the end of the 120 days of follow-up, all patients showed some degree of clinical improvement. Complete regression of the lesions occurred in one case (2), and partial regression (reduction in size and/or number of lesions) was seen in four patients (80%), as seen on the corresponding figures (Figures 1A and 1B up to 5A and 5B).

DISCUSSION

According to Correia *et al*[2], hidrocystoma is more common in middle-aged women, epidemiology consistent with the patients in this study.

The clinical picture can be composed by single or multiple lesions.[6] In this sample, single and multiple lesions were found, however, most cases (three) had a single lesion. The most frequent location was on the lower eyelids, mainly in the external aspect, which is in accordance with the findings by Couto Junior *et al*[1] and Yaghoobi *et al*.[6] Of the five patients studied, all had at least one lesion located on the lower eyelid.

Despite the small number, our case series was larger than the articles on hidrocystoma treated with BoNT-A found in the literature. Of the 13 cases treated, only five were included for fulfilling the inclusion criteria, whereas except by Correia *et al*[2], who reported their experience with two patients, most articles report only one case treated with this method.[4,5,12,13]

Due to the lack of consensus regarding the dose to be applied, the patients did not receive standardized doses, ranging from 5U to 33U of the substance according to the number of lesions. In the literature, the total dose of botulinum toxin ranged from 4U[4] to 60U[5] (Table 2). All cases were of multiple (more than five) and small hidrocystomas. The mean dose applied was 1-4U per lesion. In this study, the cumulative dose applied of the neuromodulator did not go beyond 33U, and the mean units per lesion was around 3U, but only one patient had more than five lesions (case 3).

The procedure was well tolerated by all patients and, regarding possible side effects, pain was the transient side effect present only during the injection.

At the end of the 120 days of follow-up, the result found was complete improvement of the lesions in one case and partial improvement in four cases (80%). These results are similar to those described in the literature cited.[2,4-5,12,13]

Regarding duration of effect, in the cases described by Correia *et al*[2] and Blugerman *et al*,[13] it was of six months, and for Kontochristopoulos *et al*,[5] the time of clinical response was four months. Since the follow-up of the patients in this study was only of 120 days (16 weeks), the precise durability of the effect of the neurotoxin could not be determined, and a longer follow-up is needed according to the literature, recurrence already takes place between two to six weeks after the application.[4,11,15,16]

Differently to the cases of complete resolution described in the literature, most individuals in this study achieved partial

Table 1: Cases and doses

	Age	Sex	Phototype	1ª session	2ª session
Case 1	68	Male	VI	7U Single lesion	After 15 days: 5U
Case 2	50	Female	I	5U Single lesion	_____
Case 3	53	Female	V	11U More than 30 lesions	After 30 days: 22U
Case 4	45	Female	IV	7,5U Two lesions	_____
Case 5	73	Female	IV	3U Single lesion	After 15 days: 3U

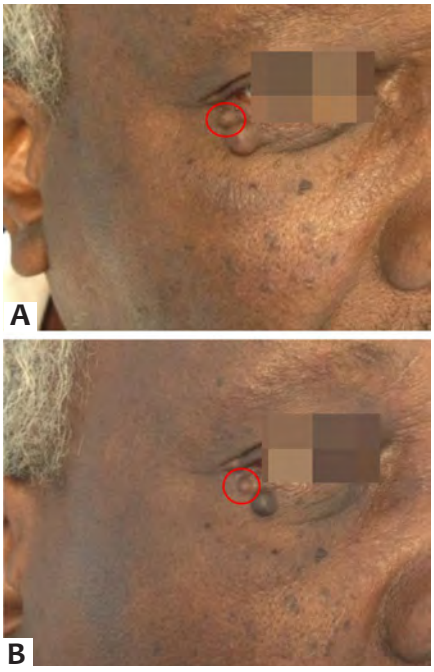


Figure 1: A e B – Reduction of the size of single hidrocystoma on the lower eyelid, adjacent to a nevus. A before, B after the toxin

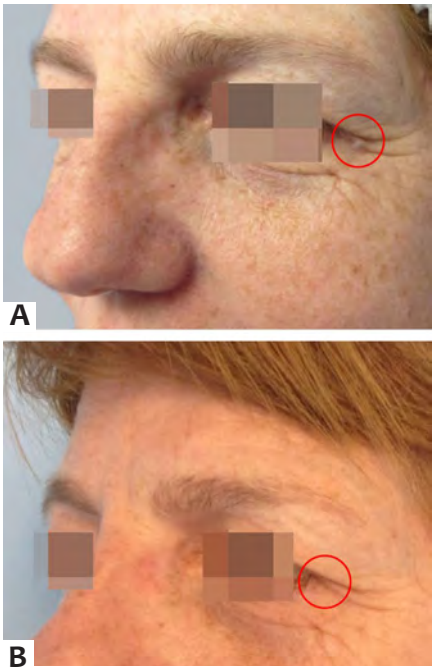


Figure 2: A – Before **B –** Complete disappearance of the lesion after treatment with the toxin

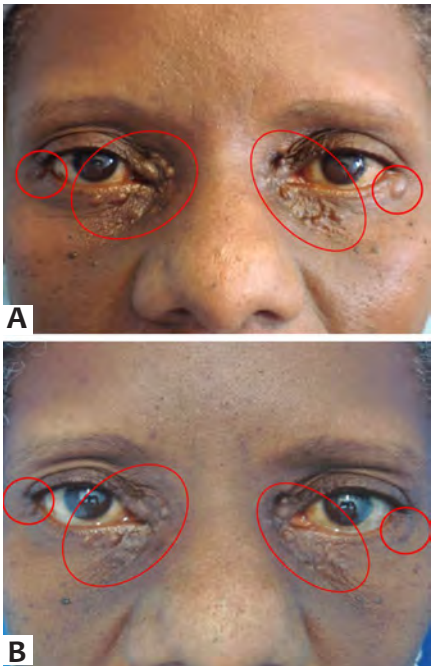


Figure 3: A - Multiple hidrocystomas of varying sizes and recurrent on the upper and lower eyelids of this patient **B –** After the toxin: marked reduction in the number and size of the lesions

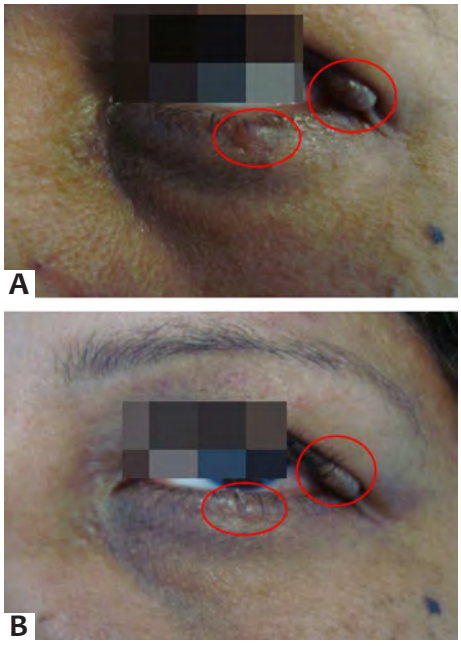


Figure 4: Female patient with lesions on the L lower eyelid. **A –** Before **B –** reduction of the size of the lesions after the toxin

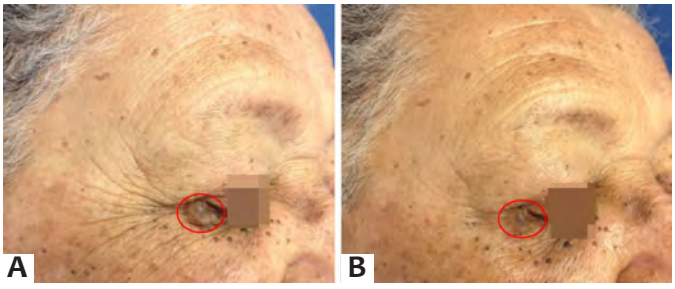


Figure 5: A – Large hidrocystoma on the R lower eyelid of this lady **B –** marked reduction after injection of botulinum toxin

Table 2: Cases found in the literature

Author	Number of cases	1ª session	2ª session
Correia *et al.*[2]	2 cases	50U Multiple lesions	_____
Meys e Perett[4]	1 case	2,5U five lesions	After two months: 1.5U
Kontochristopoulos *et al.*[5]	1 case	60U Multiple lesions	_____
Bordelon *et al.*[16]	1 case	20U Multiple lesions	After eight months: 20U
Blugerman *et al.*[13]	1 case	5U Divided in two areas	10U

improvement of the lesions. However, a detailed observation of the clinical photographs of the references cited shows that the size of the lesions in this sample was much larger than the cases described in the literature (Figures 6A and 6B).

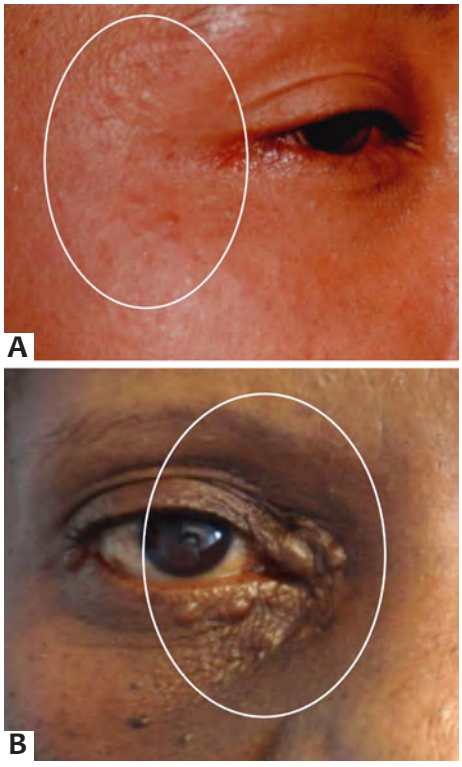


Figure 6: A - Case described by Blugerman com multiple small hidrocystomas **B –** size of the lesions in our cases

The main limitation of this article was not having a precise measurement of the diameter of each lesion identified. Thus, it is not possible to correlate the dose of toxin per millimeter of lesion, and not possible to estimate the ideal dose for each size of hidrocystoma. However, it is worth highlighting that the precise size of the lesions was also not specified in the articles here mentioned. When compared to other available treatment modalities (surgical excision, electrodessication, carbon dioxide laser, caustics), the toxin has advantages: besides good healing post-procedure, has no risk of unsightly scars or dyspigmentation. This is extremely important because hidrocystomas are mainly localized on the face, and a scar on that part of the body can be more disfiguring than the lesion itself, affecting the patient's quality of life.

CONCLUSION

Despite being benign, the disfiguring and recurrent nature of hidrocystomas are elements that need to be pondered in the therapeutic choice. Botulinum toxin is an outpatient procedure, was well tolerated and However, it is worth highlighting that along this period there were no new lesions nor increase in the size of the lesions treated, what already shows superiority of the toxin over emptying the lesions with a needle. In these cases, proved capable of reducing the size and number of hidrocystoma lesions in this case series. It can be considered as a treatment option when compared to traditional methods that present risks for scarring and/or dyspigmentation. Considering there is no standard dose in the literature for the application of this neuromodulator, nor the number of sessions needed, patients should be evaluated individually considering the location, size, number and aesthetic impact of each lesion. ●

REFERENCES

1. Couto Júnior AS, Batista GM, Calafiori IG, Radael VC, Mendes WB. Hidrocystoma: surgical management of cystic lesions of the eyelid. An Bras Dermatol. 2010;85(3):368-71.
2. Correia O, Duarte AF, Barros AM, Rocha N. Multiple eccrine hidrocystomas – from diagnosis to treatment: the role of dermatoscopy and botulinum toxin. Dermatology. 2009;219(1):77-9.
3. Vani D, Dayananda TR, Bharathi M, Hareesh RSK, Ravikumar V. Multiple apocrine hidrocystomas: a case report. J Clin Diagn Res. 2013; 7(1): 171-2.
4. Meys R, Perrett CM. Treatment of multiple periocular eccrine hidrocystoma: is botulinum toxin or electrocautery more effective? Clin Exp Dermatol. 2015;40(1):101-3.
5. Kontochristopoulos G, Markantoni V, Stefanaki C, Kanelleas A, Rigopoulos D, Gregoriou S. Multiple eccrine hidrocystomas treated with botulinum toxin A. Clin Exp Dermatol. 2010;36(1):95-6.
6. Yaghoobi R, Saboktain M, Feily A, Mehri M. Bilateral multiple apocri- ne hidrocystoma of the eyelids. Acta Dermatovenerol Alp Pannonica Adriat. 2009;18(3):138-40.
7. Schellini AS, Pinto APC, Marques MEA, Castilho CN, Achilles AB, Padovani CR. Eyelid eccrine and apocrine hidrocystoma – Occurrence at the "Faculdade de Medicina de Botucatu - São Paulo. An Bras Dermatol. 2001;76(3):283-8.
8. Verma SB. Multiple apocrine hidrocystomas: a confusing clinical diagnosis. An Bras Dermatol. 2010;85(2):260-3.
9. Sarabi K, Khachemoune A. Hidrocystomas – A Brief Review. MedGenMed. 2006;8(3):57.
10. Sampaio SA. Definição, características, tipos e subtipos. In: Almeida ART, Hexsel DM, editors. Hiperidrose e toxina Botulínica. São Paulo: Oesp Gráfica; 2003. P. 41-45.
11. Osaki TH, Osaki MH, Osaki T, Viana GA. A Minimally Invasive Approach for Apocrine Hidrocystomas of the Eyelid. Dermatol Surg. 2016;42(1):134-6.
12. Bordelon JR, Tang N, Elston D, Niedt G, Lazic Strugar T. Multiple apocrine hidrocystomas successfully treated with botulinum toxin A. Br J Dermatol. 2016;176(2):488-90.
13. Blugerman G, Schavelzon D, D' Angelo S. Hidrocistomas écrinos Múltiplos. In: Almeida ART, Hexsel DM, editors. Hiperidrose e toxina Botulínica. São Paulo: Oesp Gráfica; 2003. P. 295-8.
14. Lee MR, Ryman W. Multiple eccrine hidrocystomas. Australas J Dermatol. 2004;45(3);178-80.
15. Gupta S, Handa U, Handa S, Mohan H. The efficacy of electrosurgery and excision in treating patients with multiple apocrine hidrocystomas. Dermatol Surg. 2001;27(4):382-4.
16. Simpson LL. The origin, structure and pharmacological activity of botulinum toxin. Pharmacol Rev. 1981;33(3):155-88.

DECLARATION OF PARTICIPATION:

Ada Regina Trindade de Almeida | ORCID 0000-0002-4054-2344
Treatment and follow-up of patients. Data collection, literature review and preparation of the written text.

Jaqueline Guerra | ORCID 0000-0002-7837-9685
Data collection, literature review and preparation of the written text.

Marcelo Bellini | ORCID 0000-0002-8138-715X
Treatment and follow-up of patients.

Alessandra Romiti | ORCID 0000-0002-2231-0232
Treatment and follow-up of patients.

Maria Victoria Súarez Restrepo | ORCID 0000-0002-2614-6011
Data collection, literature review and preparation of the written text.

REALIZAÇÃO:

APOIO:

3º Simpósio Nacional de Imunobiológicos

XI Simpósio Nacional de Psoríase

São Paulo

04 de julho de 2019 | Tivoli Mofarrej | **São Paulo, SP**

Informações:
www.sbd.org.br

Civil responsibility and its consequences for the Dermatology practice

Responsabilidade civil e suas consequências no exercício da Dermatologia

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191116158

ABSTRACT

Introduction: It is estimated that in Brazil, a large number of civil responsibility lawsuits against the medical professional are in place at the courts.

Objectives: To analyze the rulings of Justice Tribunals of the Southeast and South regions of Brazil, involving dermatologists and their civil responsibility.

Methods: Definition of a research protocol on the site of the Justice Tribunals of the Southeast and South regions of Brazil.

Results: Forty-seven rulings were identified in the states of the Southeast and South regions. The main causes motivating civil responsibility of the dermatologist are linked to aesthetic procedures, to patient dissatisfaction regarding therapies chosen and to diagnostic error. Compensations sought in lawsuits against dermatologists were mostly for moral damage. Medical evaluation was requested by the judges in most lawsuits and in 87.2% the reports did not observe a causal relationship. Court decision were in favor of the dermatologists in 82.9% of the cases. It was not possible to see the full lawsuit, only the final report.

Conclusion: We can conclude that factors such as adequate training of the dermatologist, their attention to doctor-patient relationship and when filling out patient's records and documents necessary to medical practice were essential to an adequate medical evaluation, crucial to court decisions favoring dermatologists in most cases included in this study.

Keywords: Damage Liability; Dermatology; Legal Process

RESUMO

Introdução: *No Brasil estima-se que um grande número de processos de responsabilidade civil contra profissionais médicos esteja em andamento nos tribunais.*

Objetivos: *Analisar os acórdãos dos Tribunais de Justiça das regiões Sudeste e Sul do Brasil que envolvam o dermatologista e sua responsabilidade civil.*

Métodos: *Definição de protocolo de pesquisa no site dos Tribunais de Justiça dos estados da Região Sudeste e da Região Sul do Brasil.*

Resultados: *Foram identificados 47 acórdãos nesses estados. As principais causas que motivaram a responsabilidade civil do dermatologista estão ligadas aos procedimentos estéticos, à insatisfação do paciente em relação às condutas terapêuticas e ao erro diagnóstico. As indenizações solicitadas nos processos judiciais contra o dermatologista foram, em sua maioria, por danos morais. A perícia médica foi solicitada pelos juízes na maioria dos processos, e, em 87,2% das conclusões das perícias, não foi observado o nexo causal. As decisões judiciais favoráveis ao dermatologista ocorreram em 82,9% dos casos. Não foi possível conhecer na íntegra o processo judicial, mas apenas o relatório final.*

Conclusão: *Podemos concluir que fatores como a boa formação do dermatologista, sua atenção à relação médico/paciente e o cuidado ao preencher o prontuário e os documentos necessários à prática médica foram essenciais para uma perícia médica adequada e, em consequência, fundamentais para que as sentenças judiciais fossem favoráveis ao dermatologista na maioria dos casos focalizados neste estudo.*

Palavras-chave: *Dermatologia; Processo Legal; Responsabilidade Civil*

Original Articles

Authors:
Valéria Maria de Souza Framil[1]
Erika Tiemi Fukunaga[2]
Eduardo da Costa Sá[1,3]
Daniel Romero Muñoz[4,5]

[1] School of Medical Sciences, Santa Casa de São Paulo, São Paulo (SP), Brazil.
[2] Advisory Service of Statistics, Post-graduation, School of Medical Sciences, Santa Casa de São Paulo, São Paulo (SP), Brazil.
[3] Department of Occupational Medicine, Hospital das Clínicas , School of Medicine, Universidade de São Paulo, São Paulo (SP), Brazil.
[4] Discipline of Forensic Medicine, School of Medicine, Universidade de São Paulo, São Paulo (SP), Brazil.
[5] Discipline of Forensic Medicine and Bioethics, School of Medical Sciences, Santa Casa de São Paulo, São Paulo (SP), Brazil.

Correspondence:
Valéria Maria de Souza Framil
Rua Sete de abril, 296, CJ11- 1º andar
Centro
01043 -000, São Paulo, SP
Brasil
E-mail: valeriapericiamedica@gmail.com

Received on: 13/06/2016
Approved on: 26/07/2016

Study conducted at the School of Medical Sciences, Santa Casa de São Paulo (FCMSCSP) – São Paulo (SP), Brazil.

Financial support: None
Conflict of interests: None

INTRODUCTION

The expression 'medical error' refers to nothing further than the civil responsibility of the physician in front of the justice, and is used when there is an error of the physician's professional conduct regarding their patient. According to the Regional Council of Medicine of the state of São Paulo (Cremesp), the use of this expression is inadequate and should be replaced by 'medical malpractice', defined as:

Inadequate conduct that supposes a technical disregard, capable of impairing life or health injury of another, through malpractice, recklessness or negligence. This is the condition and definition of a medical malpractice, highlighting that there is no error without damage or injury to the health of others.[1]

One of the concepts of civil responsibility of the physician comes from Forensic Medicine, defined as:[1]

> *The civil, penal and administrative obligation to which physicians are subject in their professional practice when resulting in patient injury by malpractice, recklessness or negligence. This type of responsibility is based in the principle of guilt, in which the agent gives the cause for an injury, without the adequate care they are obliged to have, and does not avoid it for assuming this result will not occur.*

Some consider in the legal doctrine as 'medical error':[1]

> *The negative involuntary result, from structural flaws, when work conditions and equipment are insufficient for a satisfactory care, or medical practice that damages the patient and can be characterized as malpractice, recklessness or negligence, triggering the duty of compensation.*

Court demands appeared in a growing curve against physicians as medicine evolved, with the emergence of new specialties, innovations brought about by technologies, rise in private health care, ageing of the population and the expressive increase of the number of medical schools, some created to meet business and not social demands.[1,2]

When 'medical error' is mentioned, we can immediately associate it to a diagnostic and/or surgical or cosmetic procedure error, to the rupture of the doctor/patient relationship, to inadequate care and, lately, to the presence of mercantilism in Medicine.[1] Brazil does not have an official statistic of 'medical error', but it is estimated that a large number of civil responsibility lawsuits against the medical professional are in place at the courts.[3,4]

In 1988, the Constitution guaranteed the Brazilian citizen could obtain information of any kind regarding themselves, including the information in their medical records. And the Code of Consumers' Rights (CDC, from the Portuguese) arrived to guarantee the right to information from the supplier of products of services, that must be released to the citizen when asked for, including medical procedures.[4]

We found reports in the literature of various lawsuits that revealed the behavior of the justice regarding aesthetic procedures and surgical procedures of some medical specialties. We did not observe any such similar study regarding dermatology. Therefore, the rulings (full texts) of the justice tribunals of the Southeast and South regions of Brazil regarding civil responsibility of the dermatologist were evaluated for an initial study.

METHODS

Descriptive study based on the evaluation of lawsuits related to the civil responsibility of the dermatologist and in the research of the rulings (full texts), i.e., of lawsuits already judged, on the website of the justice tribunals of the states of the Southeast and South regions of Brazil, São Paulo, Minas Gerais, Rio de Janeiro, Espírito Santo, Rio Grande do Sul, Santa Catarina and Paraná.

The period of the research was between January 2006 and July 2015, determined according to the search on the websites of the justice tribunal under jurisprudence. The keywords used were: 'error and dermatology', 'responsibility and dermatology', 'dermatology', 'lawsuit and dermatology'.

In this study, only the court decisions related exclusively to the dermatologist in their clinical specialty, the aesthetic and surgical procedures, were included. The court decisions that involved hospitals, pathologists, health care providers, the municipality or government were not considered.

For the analysis of each ruling, a protocol with the following data was used: ruling number, year, state, damage caused, type of compensation, presence of medical expertise and e judiciary ruling related to the civil responsibility of the dermatologist. After analysis of the data collected, tables with the results found were created.

For the statistical analysis the program SPSS v.13.0 (Statistical Package for Social Sciences) was used. To verify the association between expertise and ruling, Fisher's exact test was used. All other analyses were only descriptive. In the statistical test, the level of significance of 5% was adopted.

RESULTS

The rulings or judicial decisions regarding civil responsibility of the dermatologist were obtained from the websites of the justice tribunal of each state of the Southeast and South regions.

Judicial decisions were a total of 47 rulings, and in the Southeast and South regions 37 (79.86%) and 10 (21.26%) were found, respectively. The prevalence of judicial decisions in the states of the Southeast region was of 57.44% (27 rulings) in São Paulo; 17.02% (eight rulings) in Rio de Janeiro; 5.4% (two rulings) in Minas Gerais and none in Espírito Santo. In the states of the South region we found five rulings (10.63%) both in Rio Grande do Sul and in Santa Catarina, and none in Paraná (Table 1).

The cities in which the judicial decisions of civil responsibility of the Southeast and South regions were Assis, São Paulo, Bauru, Araraquara, Campinas, Santo André, Santos, Amparo, Americana, Taubaté, São Carlos, Marília, in São Paulo; Rio de Janeiro, in Rio de Janeiro; Lavras and Belo Horizonte, in Minas Gerais; Porto Alegre, in Rio Grande do Sul; Itajaí, Florianópolis and Araranguá, in Santa Catarina.

Table 2 demonstrates the period from January 2006 to July 2015 in which judicial decisions with two peaks of increase in lawsuits in 2011 and 2014 related to the civil responsibility of the dermatologist took place, mentioned in the websites of the justice tribunal of each state of the Southeast and South regions.

The most frequent causes that motivated the patient to appeal to justice against the dermatologist, according to what is seen on table 3, were complaints in aesthetic procedures performed by dermatologists, with 46.80% (22 rulings), followed by side effects of medications (side effects) and dissatisfaction with the treatment for some dermatological conditions (acne, atopic dermatitis, viral wart, Hansen disease), with 44.57% (21 rulings), inadequate ethical conduct by the dermatologist and unidentified cases, with 4.25% of the total of rulings (two rulings).

Table 4 shows all types of aesthetic procedures involved in lawsuits according to the report of examined rulings: laser for permanent hair removal, with 14.89% (seven rulings), laser for the treatment of pigmentation, with 8.51% (four rulings), laser for wrinkles, with 4.25% (two rulings), chemical peel (freckles and pigmentation), with 6.36% (three rulings), botulinum toxin and fillers, with 4.25%, and other procedures (fillers, dermabrasion, hydrolipo and mesotherapy), with 2.12% (one ruling) each.

In table 5, medication and dermatological conditions that motivated patient complaint in lawsuits are demonstrated: vitiligo, psoriasis, actinic keratosis, warts and the drug flutamide, with 4.25% (two rulings) each. Other dermatological conditions, acne, Hansen disease, melasma, HPV, atopic dermatitis, removal of inflamed nail, systemic lupus erythematosus, herpes zoster, cryotherapy and urticaria, each with 2.12% (one ruling).

Table 1: Number of cases of judicial decisions on civil responsibility and the dermatologist in the states of the Southeast and South regions of Brazil

Southeast	**N**	**%**
São Paulo	27	57.44
Rio de Janeiro	8	17.02
Minas Gerais	2	5,4
Espírito Santo	-	-
South	**N**	**%**
Rio Grande do Sul	5	10.63
Santa Catarina	5	10.63
Paraná	-	-

Table 2: Period of time when judicial decisions occurred related to civil responsibility and the dermatologist

Ano	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
N	3	2	2	3	5	8	5	6	8	5

Table 3: Causes for judicial decisions related to civil responsibility and the dermatologist

Causes for the lawsuits	**N**	**%**
Aesthetic procedure	22	46.80
Side effects/Treatment dissatisfaction	21	44.57
Ethical conduct	2	4.25
Not identified	2	4.25

Table 6 demonstrates the medical expertise assessment for establishing the civil responsibility of the dermatologist, that happened in 83% (39 rulings). Medical experts determined in 87.2% (34 rulings) that the damage caused to the patient was related to their condition and not to the physician's practice, i.e., a causal relationship was not found. Causal relationship was confirmed in 12.8% (five rulings).

According to table 7, judicial decisions favorable to the dermatologist were in first and second instances with 80.8% (38 rulings) and 82.9% (39 rulings), respectively. Decisions unfavorable to the dermatologist in the first instance were 19.1% (nine rulings) and in second instance 17.02% (eight rulings).

Table 4: Types of aesthetic procedures involved in lawsuits according to the report of the rulings of the justice tribunal of the states of the Southeast and South regions

Type of aesthetic procedure	**N**	**%**
Laser hair removal	7	14.89
Laser wrinkles	2	4.25
Laser pigmentation	4	8.51
Chemical peel	3	6.36
Filler	1	2.12
Botulinum toxin + Filler	2	4.25
Dermabrasion	1	2.12
Hydrolipo	1	2.12
Mesotherapy	1	2.12
Total	22	46.80

Table 5: Medications and dermatological conditions involved in lawsuits - according to the report of the rulings of the justice tribunal of the states of the Southeast and South regions

Medications/Dermatological conditions	**N**	**%**
Vitiligo	2	4.25
Acne	1	2.12
Hansen disease	1	2.12
Melasma	1	2.12
HPV	1	2.12
Immunobiologic	1	2.12
Atopic dermatitis	1	2.12
Flutamide	2	4.25
Removal of inflamed nail	1	2.12
Psoriasis	2	4.25
Systemic lupus erythematosus	1	2.12
Herpes zoster	1	2.12
Cryotherapy	1	2.12
Actinic keratosis	2	4.25
Urticaria	1	2.12
Warts	2	4.25
Total	21	44.57

Data analyzed in the rulings demonstrated three types of compensation: 76.6% (36 rulings) for moral damage, 55.3% (26 rulings) material damage and 48.9% (36 rulings) for aesthetic damage (Table 8).

Judicial decisions with sentences unfavorable to the dermatologist were found in eight rulings with the amount of the compensations, that were arbitrated by the judge in five rulings (around 62.5% of unfavorable sentences) and in only three rulings (37.5% of unfavorable sentences) the amounts for compensation were not disclosed (Table 9).

DISCUSSION

The literature indicates that the number of civil lawsuits in the medical field has increased considerably over the past 10 years and, in Brazil, according to recent statistics, there was a significant increase in lawsuits against physicians.[5] The prevalence of civil judicial decisions that involve dermatologists was higher, in descending order, in São Paulo, Rio de Janeiro, Minas Gerais, Rio Grande do Sul and Santa Catarina. Regarding the states of Espírito Santo and Paraná, no rulings were found. A trend to increased number of civil lawsuits in dermatology from January 2006 to July 2015 is also observed.

Table 6: Presence of medical experts and report of medical experts regarding the presence of causal relationship in cases of civil responsibility and to the dermatologist according to the rulings report of the justice tribunal of the states in the Southeast and South regions

Medical experts	N	%
Yes	39	83
No	8	17
Causal relationship	**N**	**%**
Not confirmed	34	87.2
Confirmed	5	12.8

Table 7: Judicial decisions on the civil responsibility and dermatologist according to the rulings report of the justice tribunal of the states of the Southeast and South regions

	Judicial decisions	
	Favorable	Unfavorable
	N (%)	N (%)
First instance	38(80.8)	9 (19.10)
Second instance	39 (82.9)	8 (17.02)

Table 8: Types of compensation analyzed in rulings of the justice tribunal of the states of the Southeast and South regions

Types of compensation	N	%
Moral damage	36	76.6
Material damage	26	55.3
Aesthetic damage	23	48.9

A survey of the inquiry processes from Cremesp (Codame) was performed to determine indication of illegal ethics in the specialties of dermatology, plastic surgery and bariatric surgery, for claims of unsuccessful result proposals. In 2000, dermatology had 17 inquiry processes and, in 2007, 74 inquiry processes, characterizing a trend of increasing civil lawsuits.[5]

Judicial decisions were equivalent regarding complaints on aesthetic procedures (48.93%) and clinical dermatology (side effects of drugs and treatment dissatisfaction in some dermatological conditions, 46.80%). When we take dermatology as an essentially clinical specialty, the dermatologist takes on subjective civil responsibility or duty of due care:[6]

A good example of a duty of due care contract is the contract of health treatment, established with the physician, for the result depends on factors that are out of the professional's control, such as the physiologic nature of the patient, their reaction to drugs, among other factors. The physician is only obliged to continue pushing for their best efforts and to apply the best techniques and tools available to them to achieve the result contracted, but is not obligated to achieve it.

However, when dermatology encompasses the areas of surgical dermatology and aesthetics, it is then considered 'aesthetic' medicine, as in 'beautifying' plastic surgery and bariatric surgery. Nowadays, there is a growing intent of considering these 'result' activities.[7] Beautifying the patient is considered by lawyers, judges and the population an objective civil responsibility, considering that the contract between the two parties has as final goal the aesthetic result of the patient.[5] Lately, new concepts have become more consistent in tribunals, in view of the integration between medicine and law, and there is the understanding that aesthetic medicine is not different to curative medicine. Based on what is recommended by the World Health Organization (WHO), i.e., health is a state of complete physical, mental and social well-being, we arrive to the perception that, if the patient is uncomfortable for having facial wrinkles, they are sick. Therefore, in the field of aesthetic dermatology (cosmiatry and surgical dermatology) the principle of *Culpa Aquiliana* should be considered, i.e., the existence of negligence (omission, disregard of duties and obligations), recklessness (inattention, dangerous behavior) or malpractice (inexperience, lack of knowledge). However, there are still tribunals that consider the aesthetic procedure a relationship of result, i.e., the patient is unsatisfied with the result, and the physician is punished. The action of the professional becomes a simple contract relationship, ignoring that medicine is not an exact science and that individual features and human biology should be taken into consideration.[8]

In this study, we observed that the judge requested medical experts for most rulings (83%) evaluated for the determination of civil responsibility of the dermatologist. And that in the conclusion of medical experts, a causal relationship was not confirmed in 87% of the cases. The importance of medical experts is in identifying the anatomical, physiological, social or psychological causes related to the condition or to the procedure, aiming at finding a causal relationship between the events, for not always is medical conduct responsible for the lack of therapeutic

Table 9: Demonstrates eight favorable sentences were the amount of the compensations for aesthetic damage, material damage and moral damage were arbitrated in the sentences according to the rulings report of the justice tribunal of each state of the Southeast and South regions

Reason for claiming compensation unfavorable lawsuits	Aesthetic damage	Material damage	Moral damage	Amount arbitrated in the judiciary
Mesotherapy	R$ 10,000.00	-	R$ 15,000,00	R$ 25,000.00
Botulinum toxin/Eyelid ptosis	-	R$ 2,069.00	R$ 10,000.00	R$ 7,069.00
hair laser removal hypopigmentation	-	R$ 3,543.91	R$ 10,000.00	R$ 6,830.00
HPV	-	-	500 minimum wages	R$15,000.00
Flutamide – Acne Severe Hepatitis	-	-	R$ 15,000.00	R$ 30,000.00
Urticária	-	amount not specified	amount not specified	amount not specified
Dermatologist disputes medical expert	-	amount not specified	amount not specified	amount not specified
Permanent laser hair removal	-	amount not specified	amount not specified	amount not specified

success.[9] A well-written patient record (detailed description of the procedure and legible writing), adequate consent form and the effective doctor/patient relationship are key factors to avoid lawsuits and, consequently, the physician's emotional distress.

The medical experts will bring information necessary for the judge's verdict, for it is about a medical subject that is beyond their knowledge scope. Therefore, the medical expert that prepares the medical report should avoid subjectivity and try to stay within the specific protocols and standardizations destined to this outcome.[2]

Judicial decisions regarding the dermatologist's civil responsibility that were tried in first and second instances were 80.8% (38 rulings) and 82.9% (39 rulings), respectively. The decisions unfavorable to the dermatologist in first instance were 19.1% (nine rulings) and in second instance 17.02% (eight rulings). The difference in percentage in cases favorable to the dermatologist was due to a case in where the professional wrote psoralen cream for psoriasis and did not instruct the patient regarding caution for sun exposure, and the patient progressed to worsening of their condition following blisters and burn. The judge arbitrated unfavorable sentence in first instance and in second instance the judges considered the sentence favorable to the dermatologist. Medical experts concluded that the medication indicated is used for the treatment of psoriasis with controlled sun exposure, and that that changes that occurred in the skin did not configure aesthetic damage. Despite the medical experts not confirming the causal relationship, the first instance magistrate judged the claim well-founded, stating that:

The blame, the lack of objective duty of care, arises in the precise moment the physician, in a condition of exceptional severity, restricts the information that the time for sun exposure is of five minutes, when it would be appropriate to make available a phototherapy machine or, in case of non-existence, simply prohibiting the patient's exposure.[10]

And, in second instance, the judge was favorable to the dermatologist arguing that:

An expert opinion that confirms that the doctor acted within the possibilities and used an adequate procedure. Damage remediation. Not acceptable. Obligation of means is the obligation to employ all available techniques, tools and resources, and make all possible efforts with the aim of achieving the result contracted, regardless of this result being achieved or not. Obligation of result is the obligation to achieve the exact result contracted, regardless of the techniques and resources employed. In the obligation of means, not achieving the result contracted is a circumstance accepted in the contract and does not imply non-execution of the obligation, let alone civil responsibility. In the obligation of result, the one owing the obligation is only freed of it when the expected result is achieved, in the time and way stipulated in the contract; otherwise, they will withstand the contract's civil responsibility, if damage is a consequence of the default, of course.[10]

The same occurred in the sentences unfavorable to the dermatologist. In one case of laser hair removal, the judge in the first instance was favorable to the dermatologist and, in second instance, the judges were unfavorable, but there are no details of the case in the evaluated ruling.

The three types of compensation were 76.6% (36 rulings) for moral damage, 55.3% (26 rulings) for material damage, and 48.9% (36 rulings) for aesthetic damage. The amount requested for the compensations ranged from R$2,069.00 to R$100,000.00 or from 100 to 500 minimum wages.

The amount arbitrated by the judge in the sentences, when the Dermatologist was convicted, was not always the amount requested in the lawsuit. Some cases observed were the botulinum toxin procedure, with consequent eyelid ptosis, requesting a total amount of R$ 12,069.00. the judge arbitrated R$ 7,069.00. in a laser hair removal treatment, the total amount requested was R$ 13,543.91, and the judge arbitrated the amount of R$ 6,830.00. according to the justice:

The amount arbitrated in the case of compensation for immaterial damage should take into account the principle of proportionality, as well as the conditions of the offended, the economic capability of the offender, besides the capacity of criticizing the illicit conduct that occurred. Lastly, one must remember the compensation of damage must not turn into disproportionate gain, counting as illicit enrichment.[11]

In this study, it was observed that in one case of treatment with flutamide for acne with consequent severe hepatitis, the amount established for compensation in the lawsuit was

R$ 15,000.00, and the amount arbitrated by the judge was R$ 30,000.00.

Lawsuits generate emotional distress, besides financial losses, that can be avoided paying more attention to the doctor/patient relationship, caution in filling out necessary documents and records. According to the Code of Medical Ethics of 2009, in chapter X:

Art. 87. Refrain from creating a legible medical record for each patient.

§ 1º The medical record must contain clinical data necessary for properly directing the case, and must be filled in during each evaluation, in a chronological order with date, time, signature and number of the medical registry in the Regional Council of Medicine.

It is very important to highlight that the defense of the medical professional is based on the evolution of medical records, the signed consent form, the description of surgeries or any other document related to the medical act, that must be completed with legible writing and with no erasures.[2]

In the literature, we found studies of civil responsibility of the physician in one reflection on 'malpractice' and the relationship with disciplines that have affinity with the themes of civil responsibility, ethics, bioethics, and deontology in the state of Minas Gerais. The authors conclude that there is need for a discussion during college education regarding ethical and legal issues as a means to encompass the aspects that involve the doctor/patient relationship and avoid medical error.[8] Other authors also agree with the approach of medico-legal issues in medical schools, that could guide the future professionals in the legal and ethical aspects that encompass the professional activity.[2] According to some authors, 'it is better to prevent a lawsuit than fight against one'.[12]

CONCLUSIONS

The main causes that led the dermatologist to a lawsuit are related to aesthetic procedures, consultations involving complaints on side effects of drugs, dissatisfaction with the type of treatment for some dermatological conditions and inappropriate ethical conduct. The compensations requested in lawsuits against dermatologists were mainly for moral damage, followed by material and aesthetic damages. We can conclude that factors as good training of the dermatologist, good doctor/patient relationship and caution when filling out the medical record were essential for an adequate medical expert assessment and, consequently, judicial sentences favorable to the dermatologist in most cases presented in this study. ●

REFERENCES

1. Mansur N, Oliveira RA, coordinators. O médico e a justiça. Conselho Regional de Medicina do Estado de São Paulo: São Paulo; 2006.
2. Santos W, Solar. HP, Ventura, Ventura MP. Processos Judiciais em oftalmologia: Análise de possíveis fatores desencadeantes. Arq Bras Oftalmol. 2010;73(6):501-4.
3. Matiello FZ. Responsabilidade civil do médico. Sagra Luzzato: Porto Alegre; 2001.
4. Prestes Jr LCL, Tourinho EK, Rangel M. Análise médico-legal das demandas judiciais em imaginologia. Radiol Bras. 2012;45(2): 98-100.
5. Brandt RA, Monzillo PH. Ética em Saúde . Einstein: Educ Contin Saúde. 2007;5(4 pt 2):142-3.
6. Leocádio CAL, Cerqueira Neto EP, Branco LGB. Responsabilidade civil na gestão da qualidade. Editora Forense: Rio de Janeiro; 2005.
7. Ribeiro WC, Julio RS. Reflections on Medical Error and Medical Education in Minas Gerais State, Brazil. Rev Bras de Educação Médica. 2011;35(2):263-7.
8. Zanini M. Dermatologia e a "Culpa Aquiliana". Med Cutan Iber Lat Am. 2010;38(2):94.
9. Fujita RR, Santos LC. Denúncia por erro médico em Goiás. Rev Assoc Med Bras. 2009;55(3):283-9.
10. Brasil. Tribunal de Justiça do Rio de Janeiro (6. Câmara Cível). Acórdão nº 0000831-10.2006.8.19.0042-2010/Rio de Janeiro. Apelação Cível nº 0000831-10.2006.8.19.0042. Relator: Desembargador Nagib Slaibi, Julgado em 10 Nov 2010. Diário Oficial da União, Brasília, 10 nov. 2010.
11. Brasil. Tribunal de Justiça do Rio Grande do Sul (5. Câmara Cível). Acórdão nº 70032431777-2009/cível- Rio Grande do Sul. Apelação Cível nº 70032431777. Relator: Jorge Luiz Lopes do Canto, Julgado em 16 Dez 2009. Diário Oficial da União, Brasília, 16 dez. 2010.
12. Fenelon S. Aspecto ético-legais em Imaginologia. Radiol Bras. 2003;36(1):III-VI

DECLARATION OF PARTICIPATION:

Valéria Maria de Souza Framil | ORCID 0000-0002-8747-1926
Design and planning of the study; preparation and writing of the original; data collection, analysis and interpretation

Erika Tiemi Fukunaga | ORCID 0000-0002-9616-3765
Statistical analysis

Eduardo da Costa Sá | ORCID 0000-0001-6431-5421
Approval of the final version of the original; effective participation in mentoring the research; critical review of the literature

Daniel Romero Muñoz | ORCID 0000-0002-4042-3070
Approval of the final version of the original; critical review of the original

IV SIMPÓSIO INTERNACIONAL DE CABELOS E UNHAS DA SBD

27ª JORNADA SUL BRASILEIRA DE DERMATOLOGIA

44ª JORNADA GAÚCHA DE DERMATOLOGIA

31 de outubro e 1º e 2 de novembro de 2019

Wish Serrano Resort & Convention Gramado

Gramado • RS

Informações:
www.sbd.org.br

REALIZAÇÃO:

SOCIEDADE BRASILEIRA DE DERMATOLOGIA
SBD
MCMXII

APOIO:

SBD-RS
Sociedade Brasileira de Dermatologia
Secção RS

Histologic evaluation of the reduction of cutaneous melanin content after microneedling on the chest

Avaliação histológica da redução do conteúdo melânico cutâneo após realização de microagulhamento na região anterior do colo

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111336

ABSTRACT

Introduction: The chest is a photoexposed area that shows effects of photodamage. Microneedling is a safe option for the rejuvenation of this area, also leading to improvement in dyschromia.

Objective: To evaluate histologic cutaneous response after three monthly sessions of microneedling for the treatment of dyschromia on the chest.

Methods: Three monthly sessions of microneedling, with 1.5mm-length needles were performed, as well as skin biopsies before and 90 days after commencement of the study. Histologic samples were evaluated with H&E and Fontana-Masson stains. Melanin content was measured based on dermal *clusters*.

Results: Six patients between 38 and 67 years of age, phototypes II-III, Glogau scale II-IV were included. A positive correlation was observed between the time and dermal content of melanin ($p = 0.029$): three sessions of microneedling reduced this content on D90 compared to the beginning (6.4 ± 1.7 MC on D0 *versus* 3.1 ± 0.4 on D90, $p = 0.05$). Three patients reported global skin improvement on D90.

Conclusions: The proposed mechanism of microneedling to promote lightening includes fibroblast proliferation and neocollagenesis in the upper dermis. This is the first study to evaluate the histology of the findings associated to lightening of the chest due to microneedling.

Keywords: Histology; Melanins; Needles; Thorax

RESUMO

***Introdução**: A região anterior do tórax constitui área fotoexposta que apresenta efeitos do fotodano. O microagulhamento é opção segura para rejuvenescimento dessa área, promovendo também a melhora de discromias.*

***Objetivo:** Avaliar a resposta histológica cutânea após três sessões mensais de microagulhamento para tratamento de discromias da região anterior do tórax.*

***Métodos:** Foram realizadas, três sessões mensais de microagulhamento com agulhas de 1,5mm de comprimento, e também biópsias cutâneas antes e 90 dias após o início do estudo. As amostras histológicas foram avaliadas com as colorações de HE e Fontana-Masson. O conteúdo de melanina foi mensurado com base em clusters dérmicos.*

***Resultados:** Seis pacientes com idades entre 38 e 67 anos, fototipos II-III, escala Glogau II-IV foram incluídos. Uma correlação positiva foi observada entre o tempo e o conteúdo dérmico de melanina ($p = 0,029$): três sessões de microagulhamento reduziram esse conteúdo no D90 em comparação com o tempo inicial (6.4 ± 1.7 MC em D0 versus 3.1 ± 0.4 em D90, $p = 0.05$). Três pacientes relataram melhora global da pele no D90.*

***Conclusões:** O mecanismo proposto do microagulhamento para promover clareamento inclui proliferação de fibroblastos e neocolagênese na derme superior. Esse é o primeiro estudo a avaliar histologicamente os achados associados ao clareamento da região do tórax decorrente do microagulhamento.*

***Palavras-chave**: Agulhas; Histologia; Melaninas; Tórax*

Original Articles

Authors:
Luiza Helena Urso Pitassi[1]
Célia Luiza Petersen Vitello Kalil[2]
Clarissa Prieto Herman Reinehr[3]
Valéria Barreto Campos[4]
Christine Chaves[5]
Stela Cignachi[6]

[1] PhD in General Medicine by the Universidade Estadual de Campinas – Unicamp – Cidade Universitária Zeferino Vaz – Barão Geraldo, Campinas (SP), Brazil, CEP:13083-970
[2] Clínica Célia Kalil - Porto Alegre (RS), Brazil
[3] Master in Medical Sciences by UFRGS; dermatologist
[4] Clínica Valéria Campos – Jundiaí (SP), Brazil
[5] Farmatec – compounding pharmacy - Porto Alegre (RS), Brazil
[6] Clínica dra. Stella Dermatologista - Caxias do Sul (RS), Brazil.

Correspondence:
Clínica Célia Kalil
Rua Padre Chagas, 230
Moinhos de Vento
90570-080, Porto Alegre, RS
Brasil
Clínica Valéria Campos
Rua Barão de Teffé, 1000
Jardim Ana Maria,
13208-761, Jundiaí, SP
Brasil
E-mail: cla.reinehr@gmail.com

Received on: 13/11/2018
Approved on: 22/12/2018

Study conducted at the institution:
1. Clínica Célia Kalil - Porto Alegre, RS Brazil
2. Clínica Valéria Campos - Jundiaí, SP Brazil

Financial support: None
Conflict of interests: None

INTRODUCTION

The chest is an area that can reveal skin ageing, since it is exposed to the sun and is frequently left untreated.[1] The aspect of photodamaged skin in this region, that shows skin laxity, dyspigmentation, xerosis, wrinkles, freckles and poikiloderma leads to the patient's aesthetic dissatisfaction, who looks for effective, safe treatment options, with the shorter downtime possible.[1] In this context, the use of microneedling associated to drug delivery has been demonstrated as an effective and safe treatment, amongst the available therapeutic arsenal.

In a previous study, the authors observed positive clinical results in the overall rejuvenation of the chest with three sessions of microneedling and drug delivery, with significant improvement in the skin's texture and firmness. Besides, clinical improvement in dyspigmentation, with lightening of the treated area and achievement of even skin color was observed.[2]

The lightening effect of the technique of microneedling associated to drug delivery is described in patients with refractory melasma treated with the technique alone or associated to topical lightening agents in drug delivery, such as tranexamic acid, hydroquinone, rucinol, sophora-alpha and ascorbic acid.[3-7] Additional studies associating the lightening effect of microneedling for the treatment of the chest were not found in the literature, highlighting the need of further studies that substantiate those findings.

In this context, this study aims to evaluate the histological response observed in the skin after treatment of dyspigmentation in the region of the chest with microneedling.

METHODS

The present study aims to evaluate histologically the procedure of skin microneedling on the region of the chest. The patients were evaluated before the procedure (D0) and after three monthly sessions (D90).

The study was set up according to good quality procedures and knowledge of the participants, who signed a consent form, the patients were randomly included in the study. The exclusion criteria involved past history of keloid scar, use of isotretinoin, treatment with steroids or anticoagulants, collagen vascular disease, presence of skin infection in the treatment area, skin cancer, warts and pregnancy. Besides, patients were advised to discontinue medications and/or herbal products that could affect blood coagulation, such as aspirin, vitamin E, gingko biloba, garlic capsules, ginseng and ginger for at least 3 days before each procedure of microneedling.

The procedure of microneedling

As preparation for the procedure of microneedling, the participants were submitted to marking of the chest area shaped as an inverted triangle, where the line of the base of the triangle has as reference points the external aspect of the right and left clavicles, and the top of the triangle converges to the intermammillary center, delineating the area of the procedure (Figure 1).

After marking, the region to be treated with microneedling was prepared with topical anesthetic (lidocaine gel 23% and tetracaine 7%) one hour prior to the procedure. With the region anesthetized, the gel was removed with 0.2% chlorhexidine solution and a qualified dermatologist performed the procedure of microneedling with the device Dr. Roller® (Anvisa registration/MS: 80669600001, imported and distributed by the company MTO), a medical device made of 192 0.07mm-width and 1.5mm-length surgical steel microneedles arranged in a cylinder (figure 2). The application technique consists in, with one of the hands, positioning it in a 45° angle over the area to be treated and, with minimal pressure, performing 10 movements in four direction: horizontal, vertical, right diagonal and left diagonal. Rolling the device leads to penetration of the needles many times in the skin, causing microlesions that allow for the release of growth factors and, therefore tissue remodeling.

Immediately after the procedure, the skin was cleaned with 0.9% saline. The participants were instructed to clean the area daily with soap and apply a complementary product with mineral (inorganic) sunscreen SPF30/PPD 11.7 straight away, zinc oxide and silicone based.

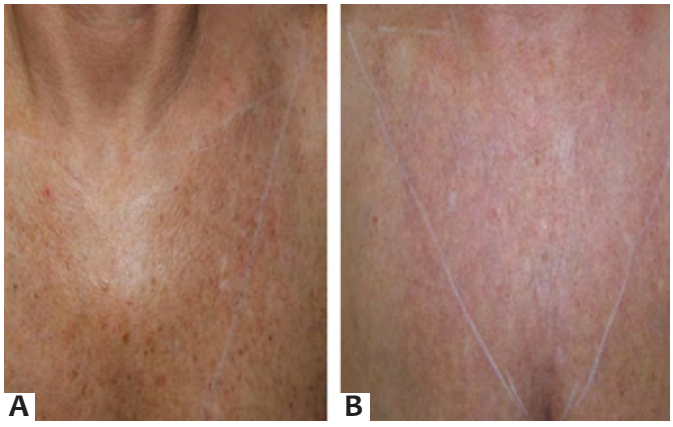


Figure 1: Area of the chest as an inverted triangle **A –** Before (D0) and **B -** After (D90) the application of the procedure of microneedling

Figure 2: medical device Dr. Roller® used to perform the procedure of microneedling

Histological evaluation of skin samples on D0 and D90

With the aim of evaluating microscopic changes induced by microneedling, biopsies of the region treated were obtained with 4mm punches, of each of the 6 patients before and three months after starting treatment. Both areas biopsied on D0 and D90 were located 1cm medially to the middle third of the right side of the inverted triangle and 0.5cm away from the previous biopsy (Figure 3). (Figure 2). Finalizing the procedure, the skin was sutured with Mononylon 5-0 suture.

The skin samples collected on D0 and D90 were fixated in 10% formaldehyde solution and incorporated into paraffin. They then underwent histological cuts of 3μm and were processed using the universal staining hematoxylin-eosin (HE). In the histological slides, inflammatory and actinic lesions were excluded, and the quantity and distribution of melanin were identified in an imprecise manner.

The histochemical reaction of Fontana-Masson (FM) was also performed, which is specific for the identification of melanin, naturally showing a tan/brown coloration, but as showing black with this reaction, which makes its identification easier. With the aim of demonstrating the overall aspect of the quality of the staining, photomicrography of the FM staining was performed with 100x magnification (Figure 4).

The FM reaction allowed for the categorization of the distribution and the amount of melanin in the skin's microarchitecture. Regarding distribution, two compartments were considered: papillary dermis and reticular dermis. To obtain the amount of melanin, the amount of melanin clusters was considered (MC) distributed along the dermis. For counting the MC, microscopic fields with 400x magnification were used (HPF, high power fields). For final identification of the amount of MC in each sample, the mean MC/HPF was considered. Therefore, the global mean papillary and reticular of MC/HPF in groups D0 and D90 was determined.

Subjective evaluation

The subjective evaluation was performed through a structured questionnaire individually answered by all patients on D30 and D90, based on their perception of the treated area regarding the following aspects: texture, wrinkles, color, shine, smoothness, firmness and overall appearance. The answers were classified into 4 scales regarding the improvement in the skin of the area treated: 1 – none; 2 – little; 3 – a lot; 4 – very much. Besides, it was also informed if the patient noticed 'any improvement with the treatment' and the answers were classified as: 1 – no; 2 – yes.

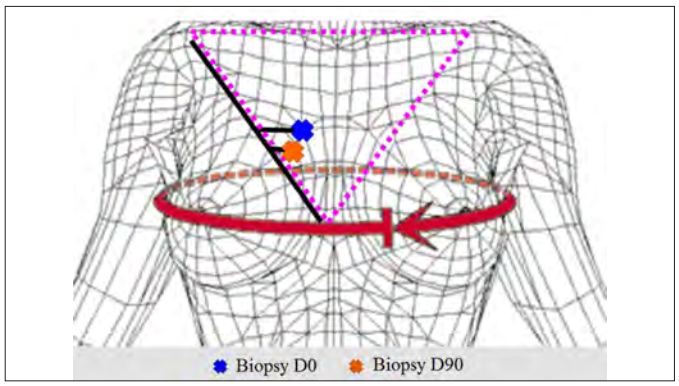


Figure 3: Areas biopsied on Do and D90

STATISTICAL ANALYSES

Data were analyzed using the statistical software SPSS version 21, IBM Corporation. Quantitative variables were compared between D0 (before) and D90 (after) by GEE and post hoc comparison of Bonferroni. To evaluate differences in qualitative variables, Fisher's exact test was performed. $P < 0.05$ was considered statistically significant.

RESULTS

Six healthy Caucasian patients, with ages between 38 and 67 years, Fitzpatrick phototype II and III, and Glogau ageing scale between II and IV participated in the study (Table 1).

Histological evaluation of skin samples on D0 and D90

There was significant interaction between the effect of time and the type of dermis ($p = 0.029$), therefore, it was verified that three sessions of microneedling (D90) tend to reduce the mean melanin clusters (MC) in the reticular dermis in comparison to the baseline mean (D0) (6.4 ± 1.7 went down to $3,.1 \pm 0.4$, $p = 0.05$). Figure 5 shows histological images before (D0) and after (D90) treatment. There was no statistically significant difference regarding MC means in the papillary dermis in the two intervals ($p = 0.47$).

Subjective evaluation

Of the six patients, three reported improvement of the skin on D90; however, this improvement was not statistically

Table 1: Baseline characteristics of the sample

	n = 6
Age – years (M±SD)	55.2±11
Gender – Female (n;%)	6; 100
Phototype* (n;%)	
II	2;33,3
III	3;50
Ageing scale**(n;%)	
II	1;16,7
III	2;33,3
IV	1;16,7
Smoking – No (n;%)	6, 100
Hormone use – No (n;%)	5;83,3
Menopause – No (n;%)	3;50
Previous treatment – No (n;%)	5;83,3

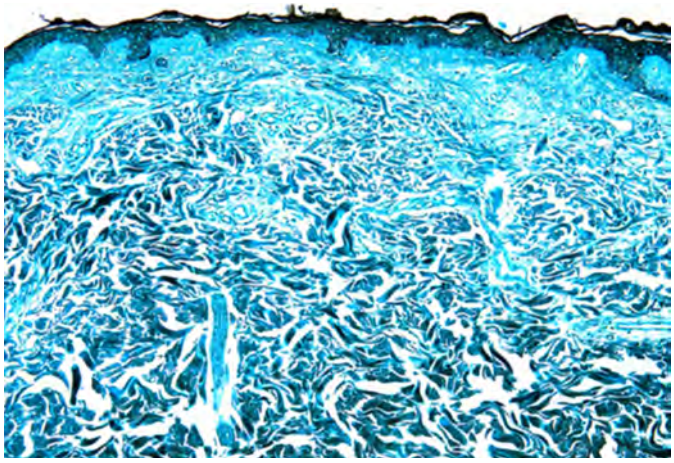


Figure 4: Photomicrography of FM staining with x100 magnification demonstrating the overall aspect of the quality of the staining

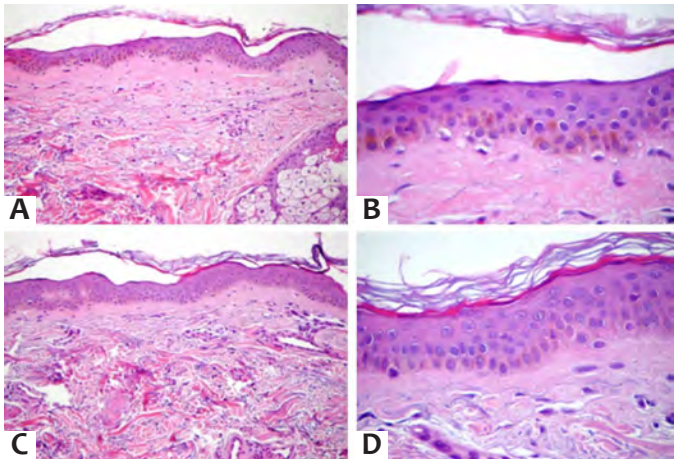


Figure 5: A - B: Pre-treatment biopsy of a phototype II patient. In this image, histology shows a significant number of melanocytes in the basal layer of the skin. Images were stained with Hematoxylin & eosin (original magnification x40); **C-D:** Histological analysis three months after treatment suggesting a reduction of the number of melanocytes with improved skin pigmentation in the areas treated with microneedling. The reduction of melanin seems to be relatively homogeneous in the extension of the epidermis evaluated (original magnification x20)

significant ($p = 0.256$) when compared to the results on D30. Two patients did not observe improvements on the area with treatment on D90 and one did not complete the questionnaire at the end of the study.

Three patients showed some kind of symptoms on the region soon after treatment with the roller, among them: erythema, erythema with burning sensation and excessive skin dryness with mild burning sensation.

DISCUSSION

Procedures that stimulate regenerative mechanisms of the body and activate injury healing in the treated skin without wound formation has been the focus of clinical research for a variety of skin conditions. The use of microneedles for percutaneous induction of collagen arises from microinjuries that reach the papillary and reticular dermis; to reach the dermis it is necessary a minimum length of the needles of 1.5mm.[8] As final result, there is partial disruption of the skin barrier, and cytokines are released, as interleukin-1-alpha, interleukin-8, interleukin-6, TNF-alpha e GM-SCF. Five days after the injury, a fibronectin matrix is formed, and the deposition of collagen is initiated, initially composed of type III collagen, subsequently replaced by type I collagen.[8,9]

El-Domyati *et al.*[10] studied the effect of microneedling with 1mm needles for facial rejuvenation in 10 patients submitted to 6 sessions of microneedling every 2 weeks, observing clinical improvement in skin ageing with correspondent histological improvement: statistically significant ($p < 0.05$) increase in epidermal thickening with better formation of the papillary dermis.[10] After the sessions, the patients presented erythema and edema, that settled over two days.[10]

Results of another study, in which 22 patients with refractory melasma, unresponsive to topical bleaching agents and sunscreen were treated with two sessions of microneedling every 30 days, demonstrating that 100% of patients reported satisfaction with the area treated after the end of the treatment protocol.[4] The author concluded that microneedling with 1.5mm length needles can lighten skin blotches in patients with refractory melasma and that the use of skin bleaching agents and e sunscreen is mandatory after the procedure.[4] Another study by the same author conducted two monthly sessions of microneedling in six women with refractory facial melasma.[7] The study demonstrated improvement of melasma in all patients, and histological analyses showed epithelial thickening, reduction of epithelial melanin pigmentation and densification of collagen in the upper dermis. The mechanism of action proposed, by which microneedling promotes improvement of hyperpigmentation such as melasma, includes fibroblast proliferation and neocollagenesis in the upper portion of the dermis.[7] These events would restore the damage to the basement membrane and in the upper portion of the dermis, avoiding the contact of melanocytes with dermal melanogenic stimuli.[11,12] Besides, once microneedling causes epidermal thickening, the procedure would promote an additional protection to UV radiation.[7]

Until now, evidence-based treatment protocols for microneedling are not available.[13] However, microneedling is a safe option for the treatment of scars and wrinkles.[13] Besides, its effects reach a maximum benefit between eight and 24 weeks, with variations observed between the authors.[14,15]

In a recent study, 12 patients were treated with three sessions of microneedle radiofrequency (Endymed Intensif, EndyMed Ltd., Cesarea, Israel) for rejuvenation of the chest region, performed every three weeks; clinical evaluation by two blinded dermatologists using the Global Aesthetic Improvement Scale demonstrated that 67% of the patients treated showed global improvement of the area, what included improvement in wrinkles, skin texture and firmness.[16] Clinical information regarding improvement of dyspigmentation in the treated area were not mentioned by the authors.

This study endorses the literature particularly regarding the significant reduction in melanin clusters in the dermis with improved pigmentation of the skin treated with microneedling. Despite other parameters tested not showing statistical significance, the data are clinically relevant so that other studies with a larger sample can be conducted, with the aim to confirm the efficacy of this treatment. We acknowledge the small sample size as an important limitation of this study, as well as the number of treatment sessions. We identify the need for future studies with larger samples that can better represent a longer follow-up period so that it is possible to create and establish international treatment protocols for microneedling.

CONCLUSION

Microneedling has been shown as a minimally invasive treatment to promote clinical and histological improvement of melasma. Histological results obtained in this study support what was previously described in the literature and are promising regarding the efficacy of the treatment. ●

REFERENCES

1. Montagna W, Carlisle K. Structural changes in ageing skin. Br J Dermatol. 1990;122(SUPPL 35):61-70.
2. Kalil CLPV, Campos VB, Chaves CRP, Pitassi LHU, Cignach S. Comparative, randomized, double-blind study of microneedling associated with drug delivery for rejuvenating the skin of the anterior thorax region. Surg Cosmet Dermatol. 2015;7(3):211-6.
3. Budamakuntla L, Loganathan E, Suresh D, Shanmugam S, Suryanarayan S, Dongare A, et al. A randomised, open-label, comparative study of tranexamic acid microinjections and tranexamic acid with microneedling in patients with melasma. J Cutan Aesthetic Surg. 2013;6(3):139-43.
4. Lima E de A. Microneedling in facial recalcitrant melasma: report of a series of 22 cases. An Bras Dermatol. 2015;90(6):919-21.
5. Fabbrocini G, De Vita V, Fardella N, Pastore F, Annunziata MC, Mauriello MC, et al. Skin Needling to Enhance Depigmenting Serum Penetration in the Treatment of Melasma. Plast Surg Int. 2011;2011:158241.
6. Ustuner P, Balevi A, Ozdemir M. A split-face, investigator-blinded comparative study on the efficacy and safety of Q-switched Nd:YAG laser plus microneedling with vitamin C versus Q-switched Nd:YAG laser for the treatment of recalcitrant melasma. J Cosmet Laser Ther. 2017;19(7):383-90.
7. Lima EVA, Lima MMDA, Paixão MP, Miot HA. Assessment of the effects of skin microneedling as adjuvant therapy for facial melasma: a pilot study. BMC Dermatol. 2017;17(1):14.
8. Lima EVA, Lima MA, Takano D. Microneedling experimental study and classification of the resulting injury. Surg Cosmet Dermatol. 2013;5(2):110-4.
9. Kalluri H, Kolli CS, Banga AK. Characterization of Microchannels Created by Metal Microneedles: Formation and Closure. AAPS J. 2011;13(3):473- 81.
10. El-Domyati M, Barakat M, Awad S, Medhat W, El-Fakahany H, Farag H. Multiple microneedling sessions for minimally invasive facial rejuvenation: an objective assessment. Int J Dermatol. 2015;54(12):1361-9.
11. Tamega A de A, Miot HA, Moço NP, Silva MG, Marques ME, Miot LD. Gene and protein expression of oestrogen- and progesterone receptors in facial melasma and adjacent healthy skin in women. Int J Cosmet Sci.2015;37(2):222-8.
12. Lee DJ, Park K-C, Ortonne JP, Kang HY. Pendulous melanocytes: a characteristic feature of melasma and how it may occur: Correspondence. Br J Dermatol. 2012;166(3):684-6.
13. Ramaut L, Hoeksema H, Pirayesh A, Stillaert F, Monstrey S. Microneedling: Where do we stand now? A systematic review of the literature. J Plast Reconstr Aesthet Surg. 2018;71(1):1-14.
14. Fabbrocini G, De Vita V, Monfrecola A, De Padova MP, Brazzine B,Teixeira F, et al. Percutaneous collagen induction: an effective and safe treatment for post-acne scarring in different skin phototypes. J Dermatol Treat. 2014;25(2):147-52.
15. Fabbrocini G, De Vita V, Pastore F, Annunziata MC, Cacciapuoti S, Monfrecola A, et al. Collagen induction therapy for the treatment of upper lip wrinkles. J Dermatol Treat. 2012;23(2):144-52.
16. Lyons A, Roy J, Herrmann J, Chipps L. Treatment of Décolletage Photoaging With Fractional Microneedling Radiofrequency. J Drugs Dermatol. 2018;17(1):74-6.

DECLARATION OF PARTICIPATION:

Luiza Helena Urso Pitassi | ORCID 0000-0001-6646-4391
Statistical analysis, approval of the final version of the original, design and planning of the study, preparation and writing of the original, data collection, analysis and interpretation, active participation in the mentoring of the research, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the literature, critical review of the original.

Célia Luiza Petersen Vitello Kalil | ORCID 0000-0002-1294-547x
Approval of the final version of the original, design and planning of the study, data collection, analysis and interpretation, active participation in the mentoring of the research, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the literature, critical review of the manuscript.

Clarissa Prieto Herman Reinehr | ORCID 0000-0003-1811-4519
Approval of the final version of the original, design and planning of the study, preparation and writing of the manuscript, , intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the literature, critical review of the manuscript.

Valéria Barreto Campos | ORCID 0000-0002-3350-8586
Approval of the final version of the original, design and planning of the study, preparation and writing of the original, data collection, analysis and interpretation, active participation in the mentoring of the research, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the original.

Christine Chaves | ORCID 0000-0001-8861-6499
Statistical analysis, approval of the final version of the original, design and planning of the study, preparation and writing of the original, data collection, analysis and interpretation, active participation in the mentoring of the research, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the literature, critical review of the original.

Stela Cignachi | ORCID 0000-0003-3667-3197
Approval of the final version of the original, design and planning of the study, data collection, analysis and interpretation, intellectual participation in propaedeutics and/or therapeutics of the cases studied.

Lysine hydrochloride use in the prophylaxis of herpes simplex in facial technology-aided procedures

Uso do cloridrato de lisina na profilaxia do herpes simples nos procedimentos faciais com tecnologias

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111273

ABSTRACT

Introduction: Lysine is one of the essential amino acids, with a role in the prophylaxis of recurrent orolabial herpes simplex that has been demonstrated in scientific studies. Facial *resurfacing* procedures with laser and other technologies can reactivate herpes simplex.

Objective: To evaluate the incidence of cases of orolabial herpes in patients submitted to treatments with fractional ablative and non-ablative lasers and robotic microneedling, under prophylactic l-lysine.

Methods: A sample of 100 patients was selected to have prophylactic l-lysine for herpes simplex. A re-evaluation of all patients was conducted seven days after laser treatment. If herpes infection was detected, doses of oral antiviral similar to those used for herpes-zoster treatment would be prescribed, guided by the literature.

Results: Only 2% of the sample demonstrated herpes simplex after the procedure with prophylactic l-lysine. Both patients underwent ablative fractional laser treatment and had past history of herpes simplex infection.

Conclusions: Besides the low cost, l-lysine is a natural product that proved to be safe and effective for the prophylaxis of herpes simplex in *resurfacing* procedures, with a similar or lower rate of viral activation to the use of antivirals.

Keywords: Herpes Simplex; Herpes Labialis; Lysine; Laser Therapy; Lasers

RESUMO

Introdução: *A lisina é um dos aminoácidos essenciais, cuja ação na profilaxia do herpes simples recorrente orolabial tem sido demonstrada em estudos científicos. Procedimentos de resurfacing facial com laser e outras tecnologias podem reativar quadros de herpes simples.*

Objetivo: *Avaliar a incidência de casos de herpes orolabial em pacientes submetidos a tratamentos com lasers fracionados, ablativo e não ablativo, e microagulhamento robótico, em uso profilático de L-lisina.*

Métodos: *Selecionada amostra de 100 pacientes a ser submetidos a profilaxia para herpes simples com L-lisina, todos reavaliados sete dias após a sessão de laser. Caso fosse verificada infecção herpética, doses de antivirais orais equivalentes às utilizadas para o tratamento do herpes-zóster seriam prescritas, conforme orienta a literatura.*

Resultados: *Apenas 2% da amostra apresentou herpes simples após o procedimento com o uso da profilaxia com L-lisina; ambos os pacientes realizaram sessões de laser fracionado ablativo e apresentavam história prévia de infecção pelo herpes simples.*

Conclusões: *Além do baixo custo, a L-lisina é produto natural que se mostrou seguro e eficaz na profilaxia do herpes simples em procedimentos de resurfacing, apresentando taxa de reativação viral similar ou inferior às obtidas com o uso de antivirais.*

Palavras-chave: *Herpes Labial; Herpes Simples; Lasers; Lisina; Terapia a Laser*

Original Articles

Authors:
Victor Bechara de Castro[1]
Maria Eduarda Pires[1]
Paula Regazzi de Gusmão[1]
Alexandre de Almeida Filippo[1]
Manuela da Silva[1]

[1] Department of Laser, Santa Casa de Misericórdia - Rio de Janeiro (RJ), Brazil

Correspondence:
Dr. Victor Bechara de Castro
R. Santa Luzia, 206
Centro,
20020-022, Rio de Janeiro, RJ
Brasil
E-mail: becharavic@yahoo.com.br

Received on: 22/10/2018
Approved on: 22/12/2018

Study conducted at the Dermatologia Professor Rubem David Azulay, Santa Casa de Misericórdia do Rio de Janeiro – Rio de Janeiro (RJ), Brazil.

Financial support: None
Conflict of interests: None

INTRODUCTION

A L-lysine is one of the eight essential amino acids, and its activity in the prophylaxis of recurrent orolabial herpes simplex and shortening of the course of this infection has been demonstrated in scientific studies.[1] The mechanism of action involved is a result from the interaction of lysine with arginine, an essential amino acid for the replication of the herpes virus. Lysine increases renal and intestinal clearance of arginine and competes with its cell transport, besides inducing the activation of the enzyme arginase.[1]

The cycle of viral replication of herpes simplex ranges from four to 12 hours and usually results in cell death. However, the virus remains latent in neuronal cells, until the moment of its reactivation, such as in treatments of laser resurfacing.[2]

Griffith *et al* demonstrated reduction of the recurrences and of the recovery time in cases of herpes simplex when they submitted 45 patients with recurrent orolabial herpes to treatment with daily doses of lysine, 312-1200mg.[3]

Patients submitted to procedures of facial laser resurfacing are susceptible of HSV reactivation. One study with 907 patients undergoing this procedure with CO_2 laser reported an incidence of acute HSV infection of 3%, which dropped to 1% after prophylaxis with aciclovir. Data published in 2001 regarding rates of herpes simplex before the use of antivirals in these procedures are from a retrospective analysis and clinical trial with historical control. In the first, six (50%) out of 12 patients with history of orofacial herpes simplex submitted to dermabrasion or phenol chemical peel developed lesions after the procedure. In the clinical trial, prophylaxis with famciclovir was conducted in 121 patients submitted to facial CO_2 laser, using historical control of 127 patients with the same procedure, without prophylaxis, that showed a reactivation rate of 9.4%.[4,5]

The exact dose and time of treatment with l-lysine necessary to reduce episodes of orolabial herpes simplex have not been established. We must take into consideration in prophylactic treatment the time needed for reepithelization, which, after ablative fractional treatments, usually lasts from 5.5 days (Erbium-Yag) to 8.5 days (CO_2 laser).[6]

Griffith RS *et al*, in a multicentric, double-blind, case-control study, demonstrated that a daily dose of 3000 mg of L-lysine for 6 months was capable of reducing the number of episodes of orolabial herpes and the recovery time, besides reducing he severity of the symptoms.[7] In their study, Mc Cune MA *et al* saw a similar result in patients on a daily dose of 1248mg of L-lysine, even though they have not noticed reduced recovery time.[8]

The objective of this study is to evaluate the incidence of cases of orolabial herpes in patients submitted to treatments with fractional, ablative and non-ablative laser and robotic microneedling and the prophylactic use of L-lysine.

METHODS

Patients older than 18 years, who would be electively submitted to resurfacing with fractional ablative and non-ablative laser or robotic microneedling (with or without radiofrequency), that had a previous history of infection by herpes simplex virus or not, performed prophylaxis with one capsule of L-lysine 500mg three times daily with meals, starting seven days before and continuing for seven days after the procedure. A reevaluation of patients was performed seven days after the laser session. In cases where herpetic infection was detected, doses of oral antivirals equivalent to those used for the treatment of herpes-zoster were prescribed, as advised in the literature.

Exclusion criteria: Pregnancy or breastfeeding, current prophylaxis for herpes simplex with other medications, hypersensitivity to any of the components of the L-lysine formulation, those with kidney and/or liver diseases.

Local: Sector of Laser, Instituto de Dermatologia Prof. Rubem David Azulay, Santa Casa de Misericórdia do Rio de Janeiro. The research was approved by the Committee of Ethics in Research, with a sample of 100 patients.

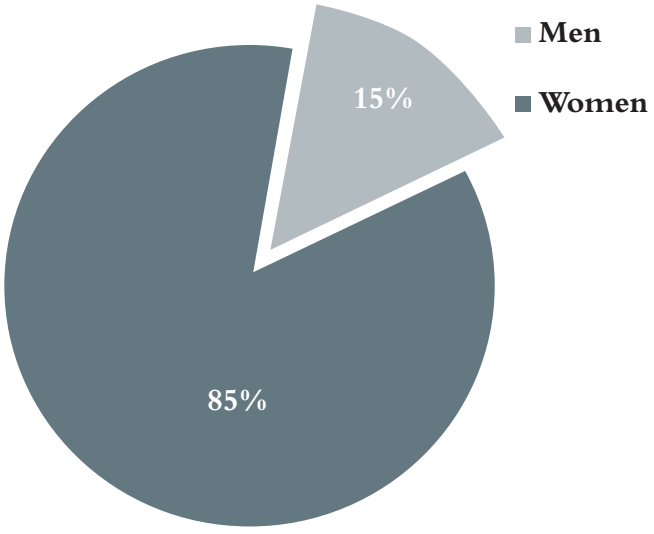
Description of the methods used to evaluate results: The evaluation of results was conducted through the clinical analysis of the cases of orolabial herpes activation, comparing them according to the procedure performed and previous history of herpes simplex.

RESULTS

One hundred patients were submitted to procedures with technologies on the face and instructed to have prophylactic L-lysine. Most of the sample was composed by females (Graph 1).

The procedure most often performed was fractional ablative laser, followed by microneedle radiofrequency and fractional non-ablative laser (Graph2).

A previous history of labial herpes simplex was reported by 21% of patients.



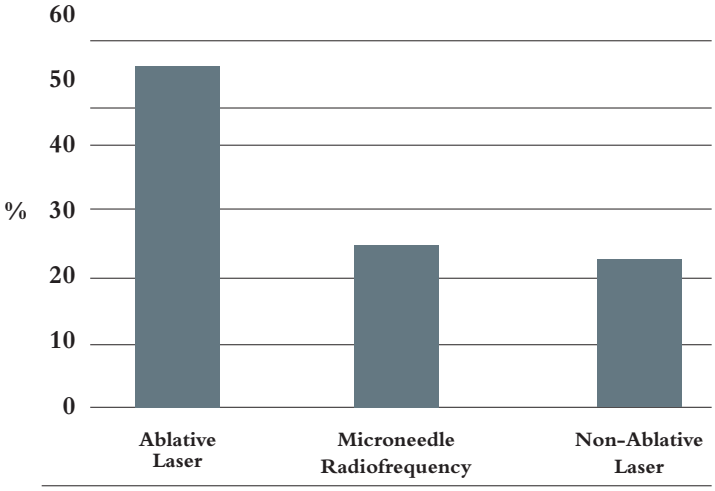
Graph 1: Sex of the patients submitted to treatment

Only 2% of the sample developed herpes simplex after the procedure with the use of prophylactic lysine hydrochloride. These patients underwent treatment with fractional ablative laser and reported previous infection by herpes simplex (Graph 3).

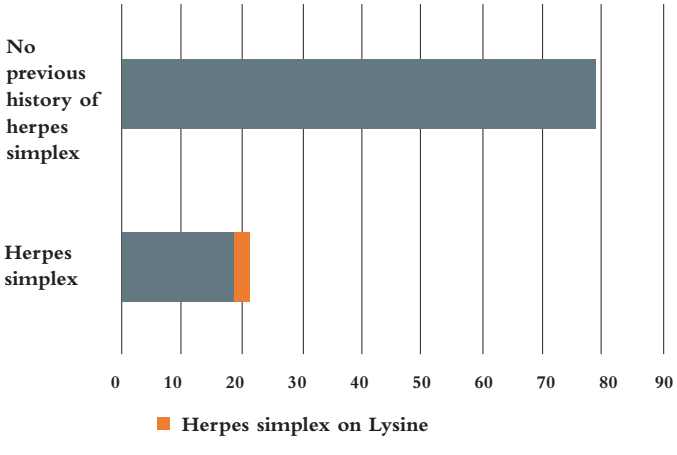
DISCUSSION

Griffit *et al*, as well as Pedrazini *et al*, showed positive results in the reduction of incidence and recurrence of herpes simplex with the administration of L-lysine for 6 months and 1 month, respectively.[7,9]

Despite the common occurrence of reactivation of herpes simplex virus after procedures of facial resurfacings, there still are no protocols in the literature for the use of L-lysine as a prophylactic agent.



GRAPH 2: Number of procedures performed



GRAPH 3 : Number of patients with and without previous history of herpes simplex and percentage of patients who had herpes simplex after the procedure

In this study, with the use of prophylactic L-lysine, we demonstrated that 2% of the patients had lesions of labial herpes simplex after procedures with technologies. These cases were mild, treated with antiviral, progressing with no unsightly scars or other complications.

Our study is in accordance with the results by Wall *et al*, where 1.1% of the patient sample that underwent sessions of CO_2 fractional ablative laser had lesions of herpes simplex even while using prophylactic famciclovir 250mg/day, started two days before and maintained for five days after the procedure. These patients had no previous history of orofacial infection by herpes simplex.[5]

The studies by Alster & Nanni and Naouri *et al*, show higher rates of complications with the appearance of herpetic lesions after fractional ablative laser. In the first, 10.1% of patients had clinical lesions consistent with herpes simplex during prophylactic famciclovir for 11 days. The second demonstrated incidence of herpes in 10.6% of patients using valaciclovir during seven days.[10,11]

In an analysis involving 730 patients submitted to sessions of fractional ablative and non-ablative lasers with prophylactic valaciclovir 500mg/day initiated 48 hours before the procedure, Cohen *et al* demonstrated the occurrence of only five cases of viral reactivation, that progressed with no formation of scars or unaesthetic outcomes.[12]

In the studies by Gilbert & McBurney, as opposed to most studies found in the literature, there were no reports of the occurrence of herpetic lesions after the procedure. However, it is worth highlighting that in this case, only laboratory criteria were used to detect the viral infection, even if there had been clinical lesions consistent with the condition. Of 84 patients analyzed by Gilbert & McBurney, 16 showed pustules/vesicles, erosions, pruritus or burning sensation after the procedure. Four of these cases grew *Staphylococcus* in culture, four had the presence of gram-negative organisms and one individual grew *Candida albicans* in culture. The other eight cases had negative viral, fungal and bacterial cultures.[13]

Most authors argument that clinically suspicious cases should be considered herpes simplex, since characteristic signs and symptoms of herpetic lesions are not found in the damaged epithelium. Moreover, traditional laboratory methods used to detect HSV (Tzanck smear, culture) might be less accurate in this scenario.[10]

No adverse events were reported associated to the use of lysine hydrochloride in our cases. On the other hand, the occurrence of nausea and headaches associated to the prophylactic use of valaciclovir and famciclovir is relatively frequent.[5]

CONCLUSION

Besides the low cost, lysine used in this study is a natural product that proved to be safe for the use as pre-procedure prophylaxis, with lower or similar rates of herpetic lesions found in the literature. Our study is pioneer, and randomized controlled clinical trials are needed to confirm the efficacy of this drug for

this purpose. However, we can conclude that L-lysine showed positive results, being a new option in the therapeutic arsenal of the dermatologist. ●

ACKNOWLEDGEMENTS

We thank the patients who committed to finishing the protocol.

REFERENCES

1. Miller CS, Foulke CN. Use of lysine in treating recurrent oral herpes simplex infections. Gen Dent. 1984; 32(6):490-3.
2. Corey, L., 2005. Herpes simplex virus. In: Mandell, G.L., Bennett, J.E., Dolan, R. (Eds.), Mandell's Principles and Practice of Infectious Diseases, sixth ed. Churchill Livingstone, New York, pp. 1762-1780.
3. Griffith RS, Norins AL, Kagan C. A multicentered study of lysine therapy in Herpes simplex infection. Dermatologica. 1978;156(5):257-67.
4. Gilbert S; Improving the outcome of facial resurfacing-prevention of herpes simplex virus type 1 reactivation, J Antimic Chemother. 2001; 47(suppl T1): 29-34.
5. Wall SH., Ramey SJ, Wall F. Famciclovir as antiviral prophylaxis in laser resurfacing procedures. Plast Reconstr Surg. 1999; 104(4):1103-8.
6. Buthani T., Batra SR, Dermatologia Cosmética, 1 edição, Rio de Janeiro, Elsevier Editora, 2009. Dispositivos ablativos, cap 7, pp 238-242
7. Griffith RS, Walsh DE, Myrmel KH, Thompson RW, Behforooz A. Success of L-lysine therapy in frequently recurrent herpes simplex infection. Treatment and prophylaxis. Dermatologica. 1987; 175(4):183-90.
8. McCune MA, Perry HO, Muller SA, O'Fallon WM. Treatment of recurrent herpes simplex infections with L-lysine monohydrochloride. Cutis. 1984; 34(4):366-73.
9. Pedrazini MC, Cury PR, Araújo VC, Wassall T. Efeito da lisina na incidência e duração das lesões de herpes labial recorrente. RGO. 2007; 55(1): 7-10.
10. Nanni CA, Alster TS. Complications of carbon dioxide laser resurfacing: an evaluation of 500 pts. Dermatol Surg. 1998; 24(3):315-20.
11. Naouri M, Delage M, Khallouf R, Georgesco G, Atlan M. CO2 fractional resurfacing: Side effects and immediate complications. Ann Dermatol Venereol. 2011; 138(1):7-10.
12. Cohen SR, Goodacre A, Lim S, Johnston J, Henssler C, Jeffers B, et al. Clinical Outcomes and Complications Associated with Fractional Lasers: A Review of 730 Patients. Aesthetic Plast Surg. 2017;41(1):171-78.
13. Gilbert S, McBurney E. Use of valacyclovir for herpes simplex virus-1 (HSV-1) prophylaxis after facial resurfacing: A randomized clinical trial of dosing regimens. Dermatol Surg. 2000; 26(1):50-4.

DECLARATION OF PARTICIPATION:

Victor Bechara de Castro | ORCID 0000-0003-1651-2919
Statistical analysis, approval of the final version of the original, design and planning of the study, preparation and writing of the original, data collection, analysis and interpretation, active participation in mentoring the research, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the literature, critical review of the original.

Maria Eduarda Pires | ORCID 0000-0002-5755-5328
Statistical analysis, approval of the final version of the original, design and planning of the study, preparation and writing of the original, data collection, analysis and interpretation, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the literature, critical review of the original.

Paula Regazzi de Gusmão | ORCID 0000-0002-7060-6062
Statistical analysis, approval of the final version of the original, design and planning of the study, preparation and writing of the original, data collection, analysis and interpretation, active participation in mentoring the research, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the literature, critical review of the original.

Alexandre de Almeida Filippo | ORCID 0000-0001-9550-5156
Statistical analysis, approval of the final version of the original, design and planning of the study, preparation and writing of the original, data collection, analysis and interpretation, active participation in mentoring the research, intellectual participation in propaedeutics and/or therapeutics of the cases studied, critical review of the literature, critical review of the original.

Manuela da Silva | ORCID 000-003-4419-5722
Preparation and writing of the original.

The use of dermoscopy of the nail plate and its free margin to help the diagnosis of onychomatricoma

O uso da dermatoscopia da placa ungueal e de sua borda livre auxiliando o diagnóstico do onicomatricoma

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.201911102

ABSTRACT

Onychomatricoma is a tumor of the nail matrix with well-known clinical features; however, sometimes underdiagnosed. It is often mistaken for onychomycosis due to thickening of the nail plate. dermoscopy of the plate and its free margin allows the visualization of important features for the diagnosis, many times not seen with the naked eye.

Keywords: Dermoscopy; Nail Diseases; Nails/Pathology; Neoplasms

RESUMO

Onicomatricoma é tumor da matriz ungueal com características clínicas bem conhecidas, porém muitas vezes subdiagnosticadas. É frequentemente confundido com onicomicose devido ao espessamento da placa ungueal. A dermatoscopia da placa e de sua borda livre permite a visualização de características importantes para o diagnóstico, muitas vezes não observadas a olho nu.

Palavras-chave: *Dermoscopia; Doença das unhas; Neoplasias; Unhas/Patologia*

INTRODUCTION

Onychomatricoma is a specific benign neoplasia of the nail apparatus and the only tumor in which the alteration of the nail plate is actively produced by the lesion. It occurs in the nail matrix with digitiform projections, causing changes in the nail. Thickening of the nail plate, longitudinal striae, yellowish staining and splinter hemorrhages are the most frequent clinical features. Clinical diagnosis is difficult not only due to the lack of knowledge about the tumor, but also when the lesion is small. Usually the nail plate lesion is mistakenly diagnosed and treated as onychomycosis. [1-3] Nail plate dermoscopy, nail clipping, ultrasonography, and magnetic resonance imaging are of assistance in the diagnosis. The treatment is surgical with the complete removal of the tumor, and anatomopathological examination defines the diagnosis.

CASE REPORTS

Case 1: A 61-year-old white female patient complaining of a lesion in the second right finger's nail that had emerged three years before. She underwent systemic and topical antifungal therapy for one year without improvement, and denied the presence of any symptom.

Clinical examination evidenced partial thickening of the nail plate on the outer side, as well as a yellowish coloration. Two points corresponding to hemorrhagic striae – which could not be seen with the naked eye – were observed by dermoscopy, as well as two small holes permeating the hyperkeratosis in the

Diagnostic imaging

Authors:
Eckart Haneke[1,2,3,4]
Nilton Di Chiacchio[5]

[1] Department of Dermatology, Inselspital Bern University Hospital, University of Bern - Bern, Switzerland
[2] Dermatology Practice Dermaticum - Freiburg, Germany
[3] Epidermis Center for Dermatology, Instituto CUF - Porto, Portugal
[4] Department of Dermatology, Ghent University Hospital - Gent, Belgium
[5] Dermatology Service, Hospital do Servidor Público Municipal de São Paulo - São Paulo (SP), Brazil.

Correspondence:
Rua Dr Cesar, 62 cj 35
02013-000, São Paulo, SP
Brazil
E-mail: ndichia@terra.com.br

Received on: 18/02/2019
Approved on: 14/03/2019

This study was performed at the Hospital do Servidor Público Municipal de São Paulo - São Paulo (SP), Brazil.

Financial support: None
Conflict of interests: None

frontal view of the free part of the nail (Figure 1). In light of these findings, the hypothesis of onychomatricoma was raised. Ultrasonography was not performed due to financial constraints. The authors of the present study chose to surgically explore the lesion and perform an anatomopathological examination, which confirmed the clinical and dermoscopic hypothesis.

Case 2: A white, 54-year-old female patient presented a yellowish color in the right thumb's nail, with absence of subjective symptoms. It was treated as onychomycosis with topical ciclopirox, followed by 250mg terbinafine daily for four months without improvement.

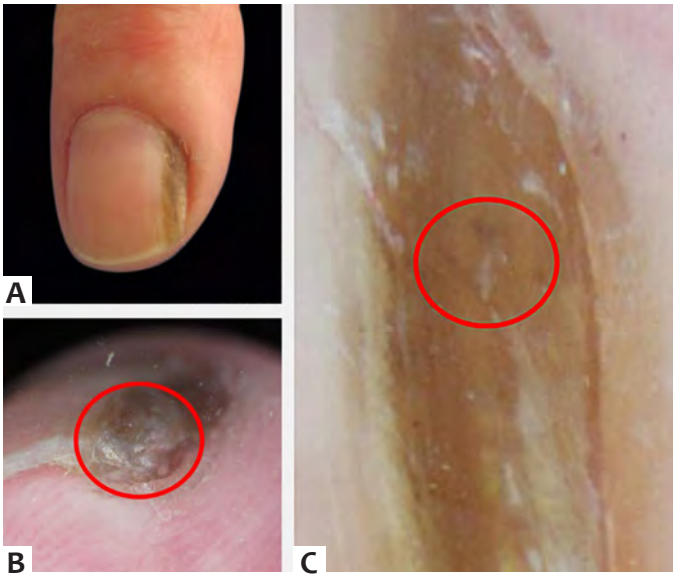


FIGURE: A - Clinical picture showing thickening of the nail plate with brownish coloration. **B -** Dermoscopy of the free border where small holes can be seen. **C -** Splinter hemorrhage not seen with the naked eye

Observation of the nail's free margin revealed circumscribed thickening with a few small holes. Dermoscopy (Figure 2) showed whitish shade of the lunula and long, stretched capillaries. This is characteristic of the tumor's digitiform projections and can reach the nail plate's holes (produced by the tumor) – and can be observed in the histological examination. Sometimes the capillaries reach the free end of the nail plate, with bleeding of the nail when it is cut.

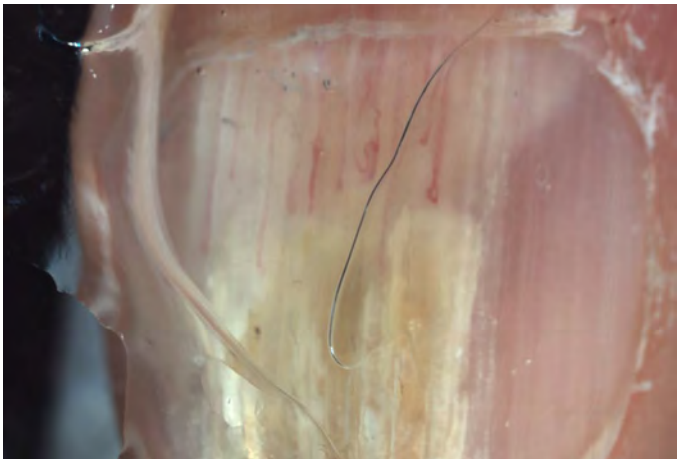


FIGURE 2: Whitish lunula with capillaries in the longitudinal direction

DISCUSSION

The diagnosis of onychomatricoma is challenging for dermatologists.[2]

In addition to the clinical alterations, nail plate dermoscopy, nail clipping,[4] ultrasonography,[5] and magnetic resonance [3] provide assistance in the diagnosis. The dermoscope is already part of the dermatological examination routine and in many times avoids expensive – and often inaccessible – tests.

The tumor originated in the nail matrix has tufted appearance with digitiform projections forming and filling cavities extending from the proximal part to the free border of the nail. This explains the holes seen in the free part of the distal plate's border, as well as the presence of capillaries in the tunnels filled by the tumor's projections. The observed hemorrhagic striae occur due to punctual bleeding of nail capillaries.[3] Dermoscopy of the nail plate provided assistance in the diagnosis in the described cases. The nail plate's yellowish coloration, hemorrhagic striae and orifices on the free border – not seen with the naked eye – became evident in Case 1. Changes in the color of the lunula and the presence of long capillaries running towards the plate's distal direction are characteristic and correspond to the tumor's digitiform projections, as observed in Case 2.

In face of the clinical findings and better visualization provided by the dermoscope, it was possible to diagnose onychomatricomas. ●

REFERENCES

1. Di Chiacchio N, Tavares GT, Tosti A, Di Chiacchio NG, Di Santis E, Alvarenga L, et al. Onychomatricoma: epidemiological and clinical findings in a large series of 30 cases. Br J Dermatol. 2015;173(5):1305-7.
2. Di Chiacchio N, Tavares GT, Padoveze EH, Bet DL, Di Chiacchio NG. Onychomatricoma. Surg Cosmet Dermatol. 2013;5(1): 10-4.
3. Richert B, André J. L'onychomatricome. Ann Dermatol Venereol. 2011; 138(1):71-4.
4. Miteva M, Farias DC, Zaiac M, Romanelli P, Tosti A. Nail clipping diagnosis of onychomatricoma. Arch Dermatol. 2011;147(9): 1117-8.
5. Soto R, Wortsman X, Corredoira Y. Onychomatricoma: Clinical and Sonographic Findings. Arch Dermatol. 2009;145(12):1461-2.

DECLARATION OF PARTICIPATION:

Eckart Haneke | ORCID 0000-0001-9957-1441
Case description, general review of the manuscript.

Nilton Di Chiacchio | ORCID 0000-0001-9536-2263
Case description, preparation of the final version and review of the manuscript.

Cryobiopsy in dermatological practice

Criobiópsia na prática dermatológica

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111217

ABSTRACT

Skin biopsy is an important introductory tool and also essential for the dermatologist. The conventional biopsy method, with the use of local anesthetics, sterile fields, surgical instruments (*punch*, scalpel, forceps, scissors) and suture material demand staff, time and considerable financial investment. Criobiopsy is a simple method, where by using the cryocautery an extraction of good quality skin fragments is made for histopathologic analysis, making it an excellent alternative to the conventional biopsies.

Keywords: Ambulatory Surgical Procedures; Biopsy; Cryosurgery; Dermatology; Histology

RESUMO

A biópsia de pele é ferramenta propedêutica importante e indispensável para o médico dermatologista. O método convencional de biópsia, com a utilização de anestésicos locais, campos estéreis, instrumental cirúrgico (punch, bisturi, pinças, tesoura) e fios de sutura, exige equipe, tempo e considerável investimento financeiro. A criobiópsia é método simples, que, por meio do criocautério, faz a extração de fragmentos de pele de boa qualidade para análise histopatológica, o que a torna excelente alternativa às biópsias convencionais.

Palavras-chave: *Biópsia; Criocirurgia; Dermatologia; Histologia; Procedimentos Cirúrgicos Ambulatoriais*

INTRODUCTION

The histological study of skin fragments is an indispensable propaedeutic method in the daily routine of dermatologists. Conventional skin biopsies require sterilized surgical instruments, operating room, nursing team and longer surgical time, as well as local anesthesia, which can cause pain and distress in patients who have phobia to needles.[1] In Brazil, there is a complicating factor since the issuance of Resolution CFM (Brazilian Federal Council of Medicine) Nº. 2,056/2013, requiring that premises where procedures using local anesthesia are carried out be furnished with minimal equipment and medication to deal with intercurrences, such as cardiorespiratory arrest and anaphylaxis – which makes mandatory that items such as emergency oxygen kits and aspirators, defibrillators, and vasoactive drugs be made available in the dermatological practice, a space in which small surgeries are performed. This requirement discourages the performance of conventional biopsies in dermatological practices. As a result, cryobiopsy becomes a good alternative to harvest cutaneous specimens to be studied.

How I do?

Authors:
Rachel de Avila Coelho[1]
Luiz Fernando de Oliveira Santana[2]
Juliana Cristina Silva Fraga[3]

[1] Department of Dermatology, Military Police Hospital - Belo Horizonte (MG), Brazil

Correspondence:
Dr. Rachel de Avila Coelho
Rua Pacífico Mascarenhas, s/n
Santa Efigênia
30110-013, Belo Horizonte, MG
Brazil
E-mail: rachelavilacoelho@yahoo.com.br

Received on: 07/07/2018
Approved on: 11/04/2019

This study was performed at the Minas Gerais Military Police Hospital - Belo Horizonte (MG), Brazil.

Financial support: None
Conflict of interests: None

Technique description

The technique consists of:

1) Topical antisepsis of the site where the cryobiopsy will be performed. [2]

2) Spraying of liquid nitrogen over the lesion from a distance of 2.5 to 3.8cm, for 4 to 5 seconds, up until the complete freezing of the lesion, visually verified based on the whitening of the region (Figure 1).[2]

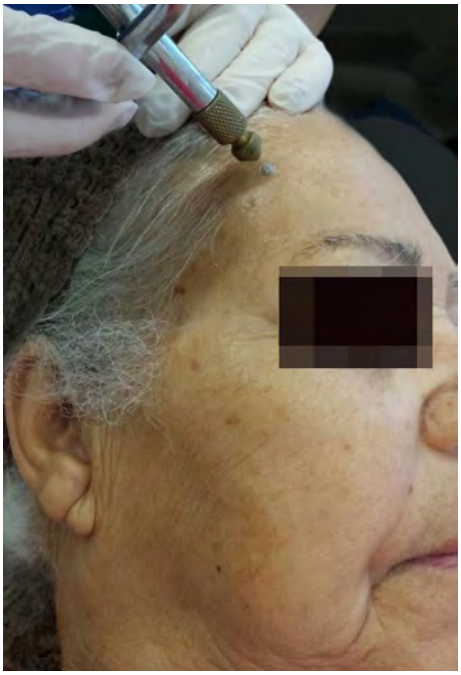


Figure 1: Spraying of liquid nitrogen on the lesion

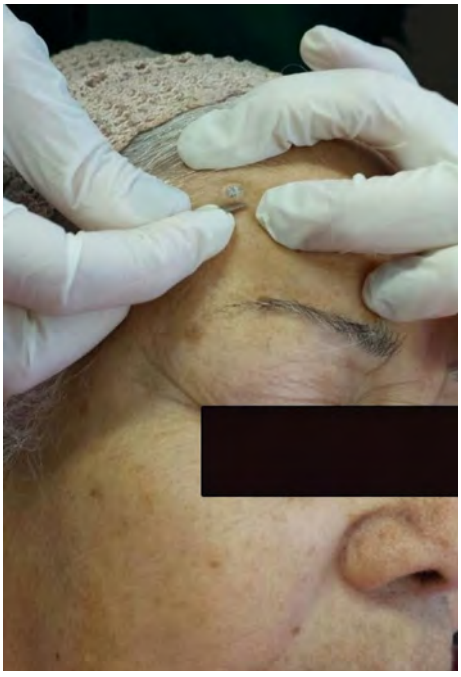


Figure 2: Shaving at the base of the lesion

3) Shaving at the base of the lesion, using a scalpel with n.15 blade, as soon as the thawing of the skin begins, while the tissue still offers some resistance (Figures 2 and 3).[2]

4) Once removed, the specimen is immediately transferred to a flask containing formaldehyde solution.[2]

5) Prior to the complete thawing of the skin, a swab soaked in 20% aluminum chloride is gently pressed onto the site for hemostasis (Figure 4).[2]

DISCUSSION

Cryobiopsy is a method used to obtain cutaneous specimens for histological analysis that uses equipment that is usually employed in dermatological practices and dismisses the use of local anesthetics and complex infrastructure to be performed.

The procedure is indicated for benign, pre-malignant lesions and non-melanoma skin cancers. Thus, the technique can

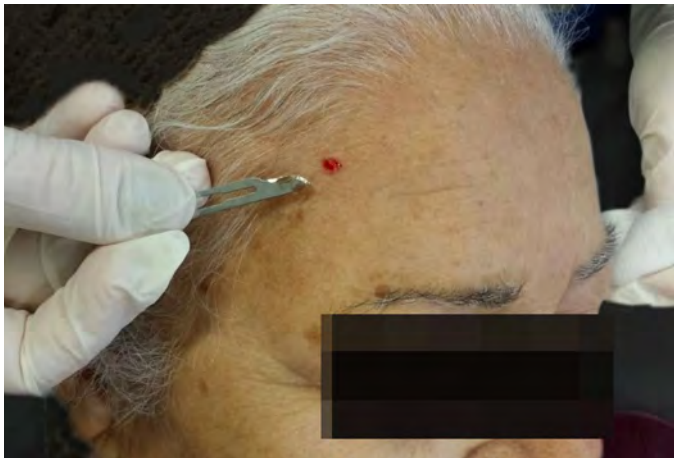


Figure 3: Complete excision of the lesion

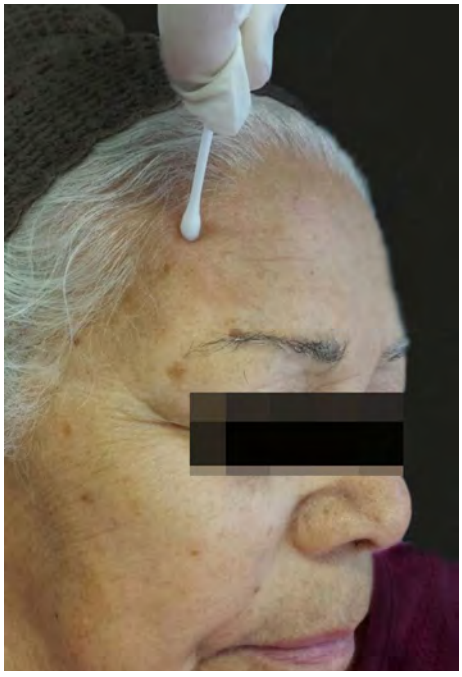


Figure 4: Local application of swab soaked in 20% aluminum chloride for hemostasis

be performed in most cases where routine biopsy is indicated (e.g. basal and squamous cell carcinomas, actinic keratoses, nevi and inflammatory or infectious lesions with dubious diagnosis – such as facial granuloma, annular granuloma, molluscum contagiosum, angiomas, soft fibromas, seborrheic keratoses, viral warts etc).[2,3]

Few conditions limit the use of cryobiopsy, which should, nevertheless, not be performed in patients with pathologies that can be induced or exacerbated by exposure to cold – such as cryoglobulinemia, Raynaud's disease, cold-induced urticaria, and previous history of cold-induced injury – or in sites with poor blood circulation.[4]

Complications arising from the procedure are usually mild and dependent on the physician's familiarity with the technique. The most common is dyschromia, in special hypopigmentation, which is the most common type due to the destruction of melanocytes caused by the low temperature.[4] In individuals with high skin phototypes, postinflammatory hyperpigmentation may also occur. The onset of depressed scars is a result of deep cryobiopsy, however it usually resolves spontaneously.[4] In hairy areas, permanent cicatricial alopecia may occur, resulting from the destruction of the hair follicle by freezing. Finally, if cryobiopsy is performed on the nail matrix or cartilage (nasal or auricular), tissue distortion may occur secondarily to the formation of indentations or retractions.[4]

Regarding the quality of the obtained skin specimen via cryobiopsy, the histological analysis of the fragments does not show any tissue damage formation or artifacts in the evaluated pieces after they have been subjected to low temperatures (Figure 5). To avoid cell autolysis, the histological specimen is placed in formalin aiming at preserving the morphology and chemical composition of the tissue's components, which contributes to a reliable histological examination.[5-7].

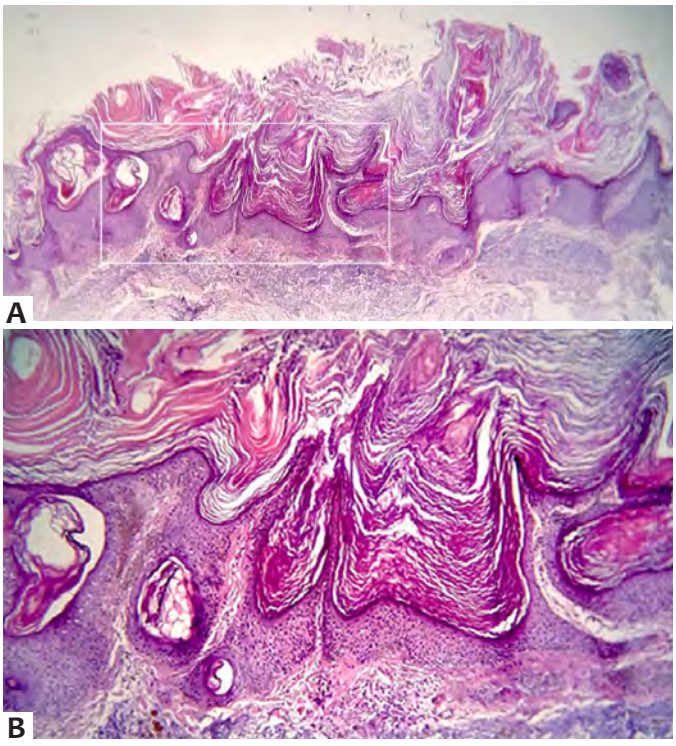


Figure 5: A - Hematoxylin & eosin cryobiopsy specimen slice under small magnification showing skin tumor characterized by hyperkeratosis, acanthosis, papillomatosis and corneal pseudocysts. **B -** Hematoxylin & eosin cryobiopsy specimen slice under greater magnification showing hyperkeratosis, acanthosis, papillomatosis, and corneal pseudocysts

CONCLUSION

The authors of the present study describe a new technique with a view to raising the awareness regarding a safe, almost painless, cost effective and efficacious procedure that can be of great value in the daily dermatological practice.

In face of the new enforced legislation, the described technique is a viable alternative to most dermatologists and provides more agility in performing skin biopsies.

The promising experience of cryobiopsies in diverse fields of medicine, such as pneumology, which has been conducting tracheobronchial biopsies since the 1980s, demonstrates how dermatological surgery can still develop and benefit from the more frequent use of this technique.[5,6,8-10]

REFERENCES

1. Pasquali P, Freites-Martinez A, Fortuño-Mar A. Cryobiopsy: Analternative technique to conventional shavebiopsy. J Am Acad Dermatol. 2015;73(5):867-8.
2. Pasquali P, Freites-Martinez A, Fortuño-Mar A. Use of cryobiopsy in dermatological practice. J Am Acad Dermatol. 2015;72(2):e63-4.
3. Pasquali P. The cryosurgery alternative. Int J Dermatol. 2007;46(5):511-3.
4. Prohaska J, Badri T. Cryotherapy. [Updated 2019 Apr 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482319/.
5. Casoni GL, Tomassetti S, Cavazza A, Colby TV, Dubini A, Ryu JH, et al. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. PLOS ONE. 2014;9(2):e86716.
6. Ohno N, Terada N, Saitoh S, ZhouH,Fujii Y, Ohno S. Recent development of in vivo cryotechnique to cryobiopsy for living animals. Histol Histopathol. 2007;22(11):1281-90.
7. Junqueira LCU, Carneiro J. Histologia Básica: texto e atlas. 4 ed. Rio de Janeiro: Editora Guanabara Koogan; 1979. p. 1.
8. Ohno N, Terada N, Bai Y, Saitoh S, Nakazawa T, Nakamura N, et al. Application of cryobiopsy to morphological and immune histochemical analyses of xenografted human lung can cert issues and functional blood vessels. Cancer. 2008;113(5):1068-79.
9. Olariu B. Endoscopic cryobiopsy in tracheobronchial pathology. Rev Chir Oncol Radiol O R L Oftalmol Stomatol Otorinolaringol. 1983;28(3):225-7.
10. Hetzel J, Hetzel M, Hasel C, Moeller P, Babiak A. Oldmeetsmodern: the use of traditional cryoprobes in the age of molecular biology. Respiration. 2008;76(2):193-7.

DECLARATION OF PARTICIPATION:

Rachel de Avila Coelho | ORCID 0000-0002-7947-7754
Approval of the final version of the manuscript, study design and planning, preparation and drafting of the manuscript, critical review.

Luiz Fernando de Oliveira Santana | ORCID 0000-0002-7793-5360
Approval of the final version of the manuscript, study design and planning, preparation and drafting of the manuscript, critical review.

Juliana Cristina Silva Fraga | ORCID 0000-0002-1593-8742
Approval of the final version of the manuscript, study design and planning, effective participation in the research guidance, intellectual participation in the propaedeutic and / or therapeutic approach of the cases studied, critical review of the literature, review of the manuscript.

Treatment of disseminated superficial actinic porokeratosis with 1,340nm Nd:YAP laser

Tratamento da poroqueratose actínica superficial disseminada com laser 1340-nm Nd:YAP

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111141

ABSTRACT

This study demonstrated the clinical and histologic result of the treatment of one disseminated superficial actinic porokeratosis patient with non-ablative fractional laser. The patient was treated with seven sessions of 1340-nm Nd:YAP laser, with 4 or 5 week-intervals. Biopsies and photographs were performed before and after treatment, which was well tolerated and lead to improvement in the erythema and texture of the lesions. There was a 1-year follow-up. Histopathologic examination after treatment revealed little changes in the cornoid lamella.

Keywords: Biopsy; Laser Therapy; Lasers; Porokeratosis

RESUMO

Este estudo demonstrou o resultado clínico e histológico do tratamento com laser fracionado não ablativo de paciente com poroqueratose actínica superficial disseminada. A paciente recebeu sete sessões de laser 1340-nm Nd:YAP, com intervalos de quatro a cinco semanas. Biópsias e fotos foram realizadas antes e após o tratamento, o qual foi bem tolerado e trouxe melhora do eritema e da textura das lesões. O seguimento foi de um ano. O exame anatomopatológico após o tratamento revelou pouca modificação da lamela cornoide.

Palavras-chave: *Biópsia; Lasers; Poroceratose; Terapia a Laser*

INTRODUCTION

Disseminated superficial actinic porokeratosis (DSAP) is a clonal proliferation of aberrant keratinocytes[1] that clinically arises as papules and erythematous or hyperchromic plaques with thin elevated borders in photoexposed body sites. [2] Ultraviolet radiation, immunosuppression and genetic factors are likely to contribute to its pathogenesis.[3]

Follow-up of these patients is necessary due to the potential malignant progression of the lesions. For symptomatic cases, there are a number of therapeutic options, such as diclofenac, calcipotriol, 5-fluoracil, imiquimod, topical and systemic retinoids, phototherapy and laser (CO_2: Er:YAG, Q-switched ruby, Q-switched Nd: 1,550nm YAG; erbium-doped, or 1,927nm thulium).[4-7]

Case Reports

Authors:
Rodolfo Ferreira Mendonça[1]
Lyvia Almeida Nascimento Salem[1]
Renata Oliveira Alves[1]
Bomi Hong[1]
Rute Facchini Lellis[2]
Elisete Isabel Crocco[3]

[1] Dermatology Service, Santa Casa de São Paulo - São Paulo (SP), Brazil.
[2] Dermatopathology Sector, Pathological Anatomy Service, Santa Casa de São Paulo - São Paulo (SP), Brazil.
[3] Acne and Cosmiatry Sector, Dermatology Service, Santa Casa de São Paulo - São Paulo (SP), Brazil.

Correspondence:
Dra. Elisete Crocco
Av. Lavandisca, 777, 10º andar
04515-011, São Paulo, SP
Brazil
E-mail: elisete@elisetecrocco.com.br

Received on: 20/01/2018
Approved on: 22/10/2018

This study was performed at the Dermatology Service, Santa Casa de São Paulo, São Paulo (SP), Brazil.

Financial support: None
Conflict of interests: None

Two case reports[5,6] evidenced clinical improvement of DSAP after treatment with fractional laser. Nevertheless, histological follow-up was not carried out. The present article describes both the clinical and histological follow-up of a DSAP case treated with 1,340 nm Nd:YAP (Neodimiun:Ytrium Aluminum Perovskite) laser, which has water as its target.

CASE REPORT

A 61-year-old woman (Fitzpatrick skin phototype II) presented erythematous-hyperchromic papules and annular plaques measuring from 3 to 12 mm, with thin hyperkeratotic borders, predominating in the legs and sparse in photoexposed areas of the thorax and forearms (Figure 1). The lesions emerged 20 years before, having been worsened in the past previous years. The patient denied pain or pruritus. The patient's mother had similar lesions and multiple cutaneous neoplasias. Histological examination revealed cornoid lamella and hypogranulosis, confirming the diagnosis of disseminated superficial actinic porokeratosis (Figure 2). After therapeutic failure with topical 0.5mg/g tretinoin in dermatological cream on alternate days for four months, the patient underwent seven 1,340 nm Nd:YAP laser sessions (Etherea®, Industra Technologies, São Carlos, SP, Brazil), with intervals of four to five weeks. Four passes per session were performed with 100mJ / MTZ, 3ms pulse duration, 100MTZ / cm^2 density and 8mm tip. Tolerance to treatment was excellent. Although new lesions have emerged during the treatment, the patient and the medical team noticed improvement of erythema and cutaneous texture after 12 months of follow-up (Figure 3). Nonetheless, after seven sessions (eight months), the anatomopathological evidenced the presence of the cornoid lamella (Figure 4).

DISCUSSION

Fractional lasers produce microscopic treatment zones, sparing the tissue that surrounds the treated column. The non-ablative property of 1,340nm laser generates fewer complications and a shorter recovery time as compared to ablative lasers. However, there is absence of literature comparing ablative and non-ablative fractional lasers in the treatment of DSAP.

Just as in other case reports where lesions were treated with non-ablative fractional laser (1,550nm and 1,927nm),[5,6] the patient was satisfied with the improvement of the treated lesions, with absence of pain or complications, except for mild erythema. Nevertheless, the intervention did not prevent the occurrence of new lesions – which continued to increase in number despite the clinical improvement.

Biopsies performed before and after treatment revealed a similar corneal lamella, hypogranulosis, and dyskeratosis. This fact does not confirm the possibility that fractional laser is capable of reducing the risk of DSAP malignant transformation, of DSAP, emphasizing the importance of the clinical follow-up.

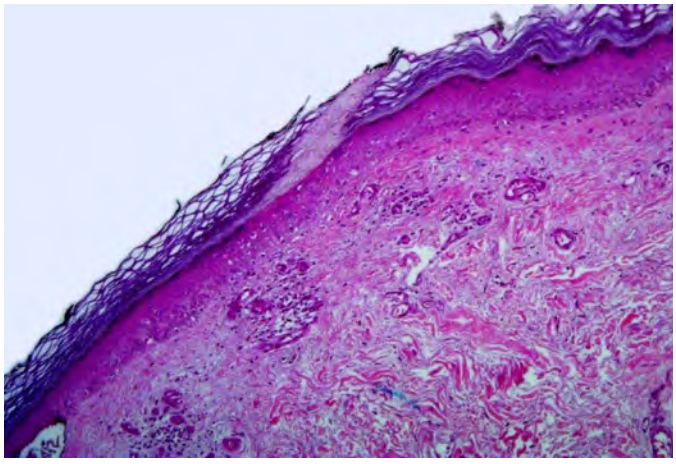


Figure 2: Histology (Hematoxylin & eosin x100) before treatment, evidencing the cornoid lamella

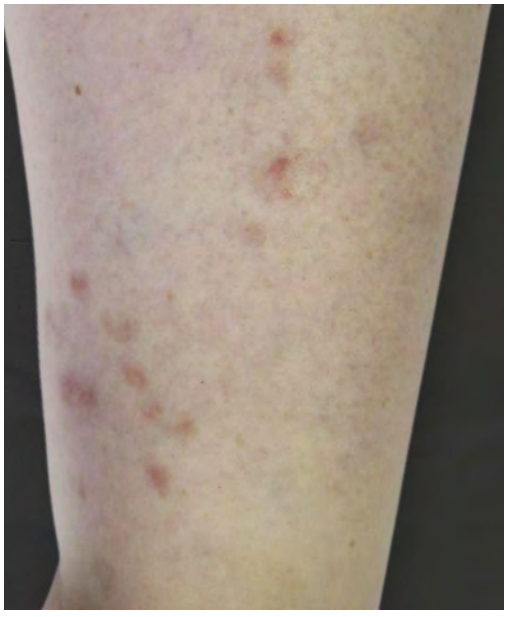


Figure 1: Active lesions of disseminated superficial actinic porokeratosis in the left leg before treatment

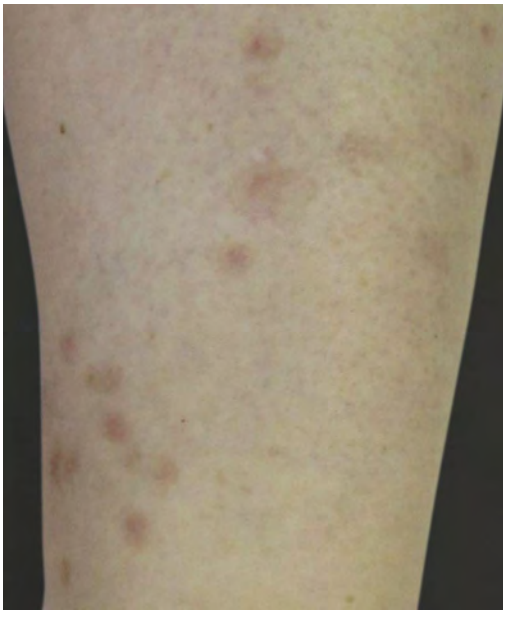


Figure 3: Left leg after 12 months of follow-up: improvement of skin texture and reduction of erythema and desquamation

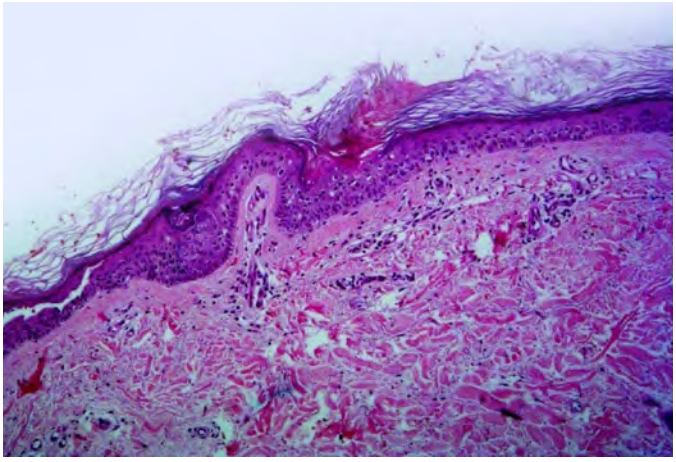


Figure 4: Histopathology (Hematoxylin & eosin x100) after treatment with fractional laser; cornoid lamella does not recede

CONCLUSION

The literature data offer a variety of therapeutic proposals with limited results for DSAP, a pathology that may bring possible risks to patients. In this way, the use of technologies becomes a potential alternative.

Despite the fact that the histologic picture did not change, treatment with 1,340nm fractional laser was proven as a well-tolerated therapeutic option for cosmetic improvement of DSAP.

REFERENCES

1. Reed RJ, Leone P. Porokeratosis - a mutant clonal keratosis of the epidermis. I. Histogenesis. Arch Dermatol. 1970;101(3):340-7.
2. Gupta G, Madan V, Lear JT. Squamous Cell Carcinoma and its Precursors. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's Textbook of Dermatology. Malden, Mass: Wiley; 2016. p. 1-46
3. Murase J, Gilliam AC. Disseminated superficial actinic porokeratosis co-existing with linear and verrucous porokeratosis in an elderly woman: Update on the genetics and clinical expression of porokeratosis. J Am Acad Dermatol. 2010;63(5):886-91.
4. Skupsky H, Skupsky J, Goldenberg G. Disseminated superficial actinic porokeratosis: a treatment review. J Dermatolog Treat. 2012;23(1):52-6.
5. Chrastil B, Glaich AS, Goldberg LH, Friedman PM. Fractional photothermolysis: a novel treatment for disseminated superficial actinic porokeratosis. Arch Dermatol. 2007;143(11):1450-2.
6. Ross NA, Rosenbaum LE, Saedi N, Arndt KA, Dover JS. Disseminated superficial actinic porokeratosis improved with fractional 1927-nm laser treatments. J Cosmet Laser Ther. 2016;18(1):53-5.
7. Aird GA, Sitenga JL, Nguyen AH, Vaudreuil A, Huerter CJ. Light and laser treatment modalities for disseminated superficial actinic porokeratosis: a systematic review. Lasers Med Sci. 2017;32(4):945-52.

DECLARATION OF PARTICIPATION:

Rodolfo Ferreira Mendonça | ORCID 0000-0003-3429-0897
Preparation of the manuscript, photographs and case follow-up.

Lyvia Almeida Nascimento Salem | ORCID 0000-0002-4277-6021
Preparation of the manuscript, photographs and case follow-up.

Renata Oliveira Alves | ORCID 0000-0001-6441-4091
Laser applications.

Bomi Hong | ORCID 0000-0003-1656-601X
Laser applications.

Rute Facchini Lellis | ORCID 0000-0001-7690-0513
Anatomopathological study and evaluation.

Elisete Isabel Crocco | ORCID 0000-0002-8844-2887
Preparation of the manuscript, case follow-up, therapeutics guidance and general supervision.

Case Reports

Authors:
Taiane Medeiros Terra[1]
Flavia Tandaya Grandi Miranda[1]
Luiz Fernando Froes Fleury Junior[1]

[1] Department of Dermatology, Universidade Federal de Goiás - Goiânia (GO), Brazil.
[2] MD, Department of Dermatology, Universidade Federal de Goiás - Goiânia (GO), Brazil
[3] MSc in Dermatology, Preceptor of Dermatological Surgery, Department of Dermatology, Universidade Federal de Goiás - Goiânia (GO), Brazil

Giant eccrine spiradenoma associated with Brooke-Splieger syndrome

Espiradenoma écrino gigante associado à síndrome de Brooke-Splieger

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111253

ABSTRACT

Brooke-Spiegler syndrome is a rare autosomal dominant genetic disease with predisposition to many adnexal tumors, including trichoepithelioma, cylindroma and spiroadenoma. Tumors appear in the second decade of life, progressively increase with age, and their prevalence is higher in women. It is caused by a mutation in the CYLD gene, localized in the chromosome 16q12-q13. We report a exuberant case of giant eccrine spiradenoma associated to this syndrome.

Keywords: Dermatologic Surgical Procedures; Facial Neoplasms; Neoplasms, Adnexal and Skin Appendage

RESUMO

A síndrome de Brooke-Spiegler é doença genética autossômica dominante rara, com predisposição a diversos tumores anexiais, dentre eles tricoepitelioma, cilindroma e espiradenoma. Os tumores surgem na segunda década de vida, aumentam progressivamente com a idade e sua prevalência é maior em mulheres. É causada por mutação no gene CYLD, localizado no cromossomo 16q12-q13. Relatamos caso exuberante de espiradenoma écrino gigante associado a essa síndrome.

Palavras-Chave: *Neoplasias Cutâneas; Neoplasias de Anexos e de Apêndices Cutâneos; Procedimentos Médicos e Cirúrgicos de Sangue*

Correspondence:
Taiane Medeiros Terra
Serviço de Dermatologia Prof. Aiçar Chaul
1ª Avenida, s/n
Setor Leste Universitário
74605-020, Goiânia, GO
Brasil
E-mail: taianemterra@gmail.com

Received on: 17/09/2018
Approved on: 17/03/2019

This study was performed at the Dermatology Service of the Universidade Federal de Goiás - Goiânia (GO), Brazil.

Financial support: None.
Conflict of interestss: None.

INTRODUCTION

The Brooke-Spiegler syndrome is a rare hereditary autosomal dominant inheritance caused by a mutation in the CYLD gene, which is located on chromosome 16q12-q13.[1]

It has the clinical appearance of cylinder type multiple adnexal tumors, trichoepithelioma and spiradenoma.[2]

The authors of the present report describe a rare case of Brooke-Spiegler syndrome associated with giant eccrine spiradenoma in the forehead.

CASE REPORT

A previously healthy 55-year-old male patient reported an eight-year the history of a progressive, slow-growing forehead mass. In addition to the aesthetic impairment, the patient complained of decreased visual field due to the lesion. At the dermatological examination, it was possible to observe a well delimited, fibroelastic, pedunculated, normochromic-reddish

and elevated frontal tumoral mass measuring 9.0x4.0x7.0cm (Figures 1 and 2). The patient had multiple small normochromic nodules on the face and scalp.

There were similar cases of multiple face nodulations in the patient's family. The lesion was excised (Figure 3) and excess skin was removed for primary closure.

Figure 4 shows the immediate postoperative period, while Figure 5 shows the 10th day after surgery. The patient was extremely satisfied with the surgical outcome.

The anatomopathological examination evidenced multiple foci of juxtaposed basaloid blocks and other clear cells located in the superficial and deep reticular dermis, forming nodules with precise and lobed borders, compressing the adjacent subcutaneous tissue and forming a pseudo-capsule. There are areas of necrosis with formation of cystic structures filled by fibrinoid and hematic material. Blind bottom ducts are also observed

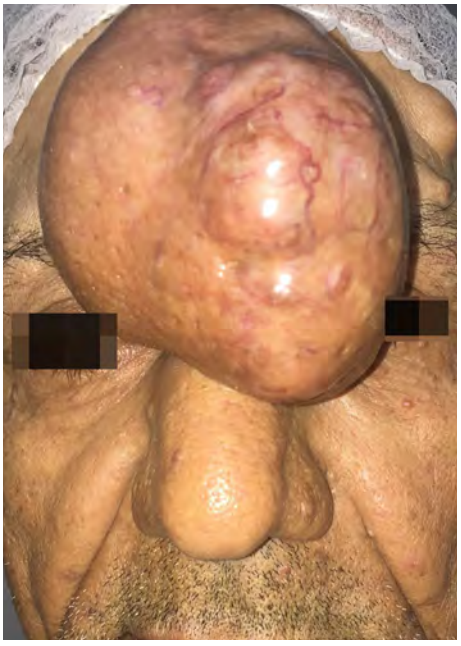


Figure 1: Normochromic, well-delimited tumor in the forehead, with vessels on the surface. Notice the minor nodulation in the left hand side of the upper forehead

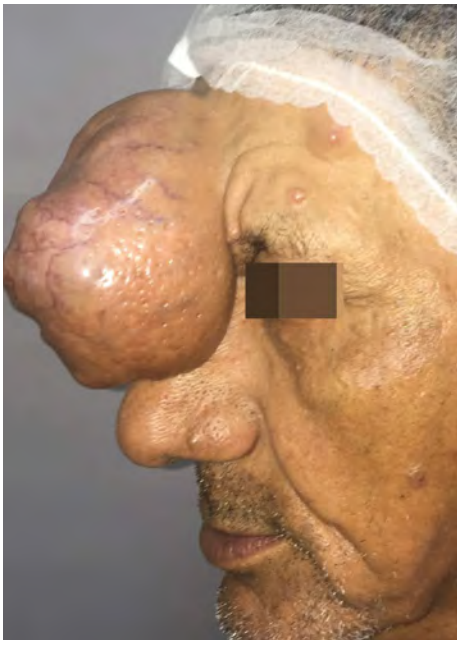


Figure 2: Lateral view of pedunculated tumor in the forehead

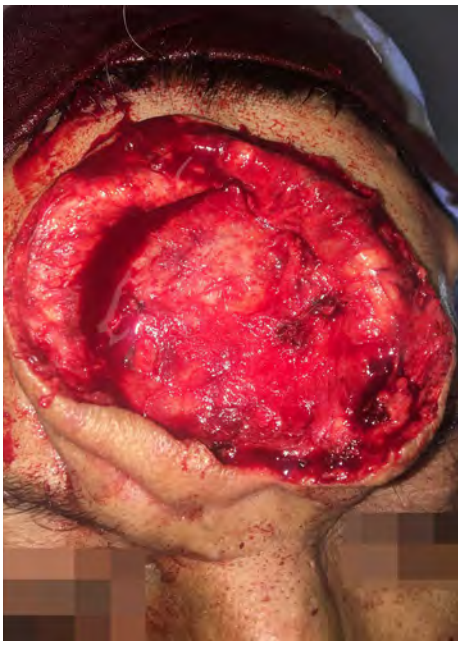


Figure 3: Image demonstrating the intraoperative period

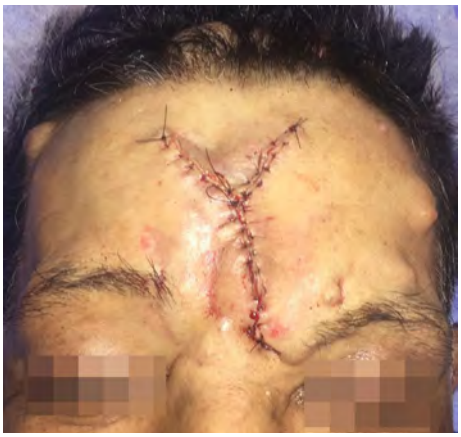


Figure 4: Immediate postoperative period

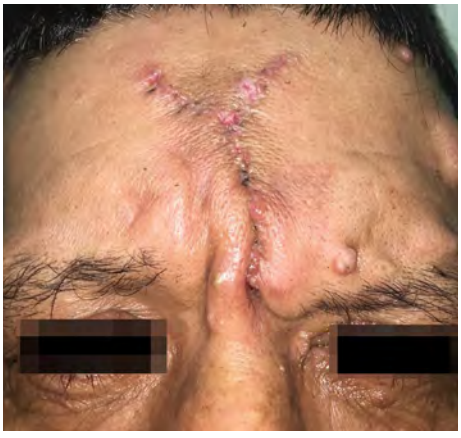


Figure 5: Tenth postoperative day

(Figures 6 and 7). Immunohistochemistry was performed for BEREP4, which came out negative, and for Ki-67, which was positive in 15% of the neoplastic cells. These findings suggest a diagnosis of eccrine spiradenoma.

DISCUSSION

The Brooke-Spiegler syndrome is a rare autosomal dominant disease characterized by the development of multiple adnexal neoplasms, including cylindroma, spiradenoma, and trichoepithelioma. [3] It was first reported in 1842 by Ancell. [2] It has higher prevalence in women.[4,5] CYLD, the gene is implicated in the pathogenesis of the disease, is a tumor suppressor gene located on the chromosome 16q12-q13. In addition to the skin, morphologically similar neoplasms may arise in the salivary glands and breasts, however this is extremely rare.[1]

Patients with Brooke-Spiegler syndrome have multiple tumors located mainly in the head and neck region. Most nodules measure 0.5 to 3.0 cm, however larger lesions can also be found[1], as in the present case.

Most of the tumors microscopically correspond to spiradenomas, cylindromas or trichoepitheliomas. They are histologically identical to sporadic cases; however, in cases of this syndrome, it is more common to find variants of multifocality of tumor types in the same lesion.

Cylindromas occur as numerous papules, nodules or tumors distributed on the scalp and sometimes on the face and trunk.[6] A classic presentation of multiple confluent lesions on the scalp is called a "turban tumor".[7] They are histologically characterized by a well-circumscribed lesion composed of tumor islands and basaloid cell cords organized in a "puzzle" pattern.[8] Malignant transformation of cylindroma is rare.

In addition to scalp lesions, patients with the classic Brooke-Spiegler syndrome phenotype have small, normochromic discrete and / or confluent papules, of 0.2 to 1.0 cm in size, located in the nasolabial folds, histologically corresponding to trichoepitheliomas. These are aggregates of basaloid cells with peripheral palisade formation, relatively monomorphic in the dermis, surrounded by fibrous stroma. Retraction artifacts and mucinous stroma are absent in this tumor.[8]

In the present case, the patient had a giant eccrine spiradenoma. This tumor is histologically characterized by cell lobes – often encapsulated and circumscribed by basaloid cells – filling the dermis. Small ductal lumens can be seen in the centers of the lobes. There is no cellular pleomorphism, and mitotic activity is sparse or absent. There can be lymphocytic infiltration into the tumor.[8]

The tumors appear mainly in the second decade of life and their quantity increases progressively with age. They grow slowly and progressively. Rapid growth associated with ulceration and bleeding should raise the suspicion of malignant transformation.[4,5] Malignant tumors arise in association with pre-existing benign cutaneous neoplasms in about 5 to 10% of patients.[1,6]

The Brooke-Spiegler syndrome, multiple familial trichoepithelioma, and familial cylindromatosis share overlapping clinical findings. While patients with Brooke-Spiegler syndrome are predisposed to multiple adnexal tumors, patients with familial cylindromatosis have only cylindromas, [2] and those with multiple familial trichoepitheliomas, only have trichoepitheliomas.[1]

The different treatment methods suggested for adnexal tumors include excision, dermabrasion, cryotherapy and CO_2 laser. For eccrine spiradenoma and cylindroma, surgery is the

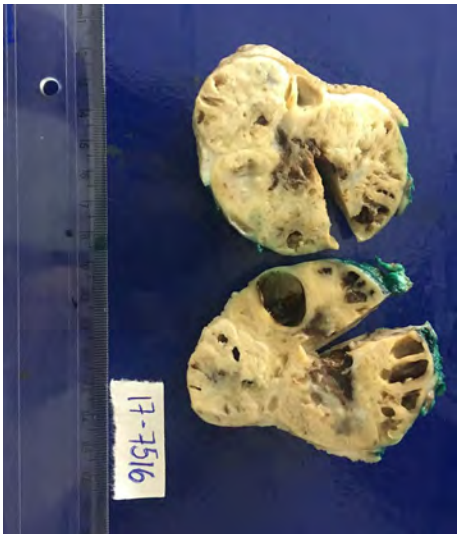


Figure 6: Surgical specimen showing a well-delimited tumor composed of cystic areas in its interior

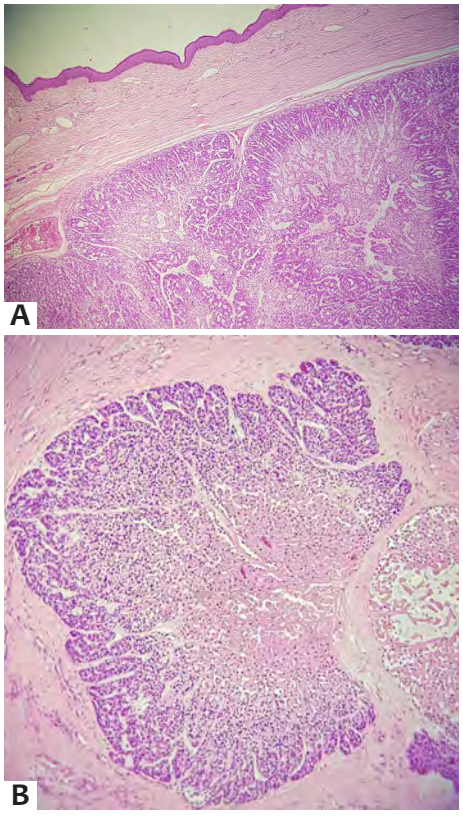


Figure 7: A - Anatomopathological examination evidencing focus of lobulated basaloid block compressing adjacent subcutaneous tissue and forming a pseudo-capsule. **B -** Pathologic examination evidencing focus of lobed basaloid block

treatment of choice. [3] In the case described in the present paper, the authors made a choice for surgical treatment due to the extension of the lesion and aesthetic compromise. Surgical treatment of eccrine spiradenoma is curative.

CONCLUSION

The Brooke-Spiegler syndrome is a rare genetic disease predisposing to adnexal cutaneous tumors. The authors of the present report describe an exuberant case of giant eccrine spiradenoma associated with this syndrome, with excellent surgical outcome. ●

ACKNOWLEDGEMENTS

The authors would like to thank all members of the Dermatology Service, Hospital das Clínicas da Universidade Federal de Goiás.

REFERENCES

1. Kazakov DV. Brooke-Spiegler Syndrome and Phenotypic Variants: An Update. Head Neck Pathol. 2016;10(2):125-30.
2. Rathi M, Awasthi S, Budania SK. Ahmad F, Dutta S, Kumar A. Brooke-Spiegler Syndrome: A Rare Entity. Case Rep Pathol. 2014;2014:231895.
3. Chen M, Liu H, Fu X, Yu Y, Yu G, Tian H, et al. Brooke-Spiegler syndrome associated with cylindroma, trichoepithelioma and eccrine spiradenoma. Int J Dermatol. 2013;52(12):1602-4.
4. Parente JNT, Schettini APM, Massone C, Parente RT, Schettini RA. Do you know this syndrome? An Bras Dermatol. 2009;84(5):547-9.
5. Kaline P, El-Azhary R. Brooke-Spiegler Syndrome with Multiple Scalp Cylindromas and Bilateral Parotid Gland Adenomas. Case Rep Radiol. 2012;2012:249583.
6. Manchanda K, Bansal M, Bhayana AA, Pandey SS. Brooke-Spiegler Syndrome: A Rare Entity. Int J Trichology. 2012;4(1):29-31.
7. Patra S, Sethuraman G, Kumar R. Turban Tumor: A Classical Presentation of Brooke-Spiegler Syndrome. Indian Dermatol Online J. 2018;9(4):284-5.
8. Brinster NK. Liu V, Diwan AH, McKee PH. Espiradenoma Ècrino. In: Brinster NK. Liu V, Diwan AH, McKee PH, editors .Dermatopatologia. Elsevier: Rio de Janeiro; 2011. p. 422.

DECLARATION OF PARTICIPATION:

Taiane Medeiros Terra | ORCID 0000-0002-6479-8686
Approval of the final version of the manuscript; study design and planning; preparation and drafting of the manuscript; intellectual participation in propaedeutic and / or therapeutic treatment of cases studied; critical review of the literature.

Flavia Tandaya Grandi Miranda | ORCID 0000-0002-4323-2499
Resident Doctor in Dermatology, Dermatology Service of the Universidade Federal de Goiás, Goiânia (GO), Brazil

Luiz Fernando Froes Fleury Junior | ORCID 0000-0002-1202-6211
Dermatologic Surgery, Dermatology Service of the Hospital das Clínicas of the Universidade Federal de Goiás

Case Reports

Authors:
Luciane Prado Silva Tavares[1,2]
Osterno Potenciano[1]
Yasmin Pugliesi[2,3]
Raissa Lelitscewa da Bela Cruz Faria[3]
Nathalia Lelitscewa da Bela Cruz Potenciano[4]
Lara Silva Paixão[5]

[1] Clínca Luciane Prado - Palmas (TO), Brazil.
[2] Clínca Luciane Prado - Palmas (TO), Brazil.
[3] Universidae Federal de Tocantins - Palmas (TO), Brazil.
[4] Centro Universitário UniEvangélica - Anápolis (GO), Brazil.
[5] Pontifícia Universidade Católica Goiás - Goiânia (GO), Brazil.

Treatment of neurofibromatosis NF-1 with CO_2 laser - Case report

Tratamento de neurofibromatose NF-1 com laser de CO_2 – Relato de caso

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111162

ABSTRACT

Type 1 neurofibromatosis has multiple cutaneous lesions and limited treatment options. CO_2 laser is a useful tool for the removal of neurofibromas, the main source of cosmetic disfiguration for these patients. We present the treatment of neurofibromas with CO_2 laser in a patient over 4.5 years. The patient had lesions with variable diameter, diffusely distributed. After 16 sessions of CO_2 laser, we observed clinical improvement. Although it is a palliative treatment, the cosmetic improvement achieved substantiates the demanded effort and time in view of the psychological gains for the patient.

Keywords: *Lasers, Gas; Laser Therapy; Neurofibromatosis 1*

RESUMO

Introdução: A neurofibromatose tipo 1 apresenta lesões cutâneas múltiplas e limitadas opções terapêuticas. O laser de CO_2 é ferramenta útil na remoção de neurofibromas, a principal fonte de desfiguração cosmética nesses pacientes. Apresentamos o tratamento de neurofibromas com laser de CO_2 em uma paciente ao longo de quatro anos e meio.

Relato do caso: A paciente apresentava lesões de diâmetro variável, distribuídas difusamente. Após 16 sessões com laser de CO_2 constatou-se melhora clínica.

Conclusão: Apesar de ser tratamento paliativo, a melhora estética obtida justifica o esforço e tempo demandados, tendo em vista os ganhos na esfera psicológica do paciente.

Palavras-chave: Lasers de Gás; Neurofibromatose 1; Terapia a Laser

Correspondence:
Av. Teotônio Segurado 101 Sul
Ed. Office Center, Salas 203/205
77015-002, Palmas, TO
Brasil
E-mail: clinicalucianeprado@gmail.com

Received on: 12/03/2018
Approved on: 24/03/2019

This study was performed at the Clinic Luciane Prado - Palmas (TO), Brazil.

Financial support: None
Conflict of interests: None

INTRODUCTION

Neurofibromatosis type I (NF1), previously known as Von Recklinghausen disease, is a dominant autosomal condition with variable incidence (1:2,500 to 1: 3,000 inhabitants). It results from loss of expression of the NF1 gene, which is responsible for the synthesis of neurofibromin, a protein that plays a role in the mechanisms that regulate cell proliferation. It is observed in all races and is unrelated to gender. Neurofibromatosis type I may involve changes (neurofibromas and cutaneous hyperpigmentation) in multiple systems, including the nervous system, bones and skin. Neurofibromas are benign peripheral nerve tumors that can be observed in 48% of patients at 10 years of age.[1-2]

The National Institutes of Health (NIH) has established a consensus on the diagnostic criteria for NF1. Two or more of the following findings are needed: six or more *café-au-lait* patches; two or more cutaneous / subcutaneous neurofibromas or one plexiform neurofibroma; axillary or inguinal ephelides;

optic glioma; two or more Lisch nodules in the eyes; dysplasia of the sphenoid bone or cortical thinning of long bones and a first degree relative with NF1. Any region of the body can be affected by cutaneous neurofibromas, which can vary in size, number and distribution. Usually they appear at puberty and continue to grow. Deformities can result from the growth of hundreds of cutaneous neurofibromas, leading to social isolation and emotional distress.[2]

The treatment of this cutaneous alteration is predominantly surgical, however alternative treatments should be considered for patients with multiple lesions – usually above 100 – in whom surgical intervention is not possible or desirable. CO_2 laser has been shown to be effective in the treatment of large to medium neurofibromas in large numbers, with similar or better aesthetic outcomes than those obtained with surgical excision. However, evidence of CO_2 effectiveness, treatment effects on patients' satisfaction, and post-treatment recurrence rate are scarce.[3-5]

The present paper describes the case of a 37-year-old patient bearing hundreds of dermatological lesions of neurofibromatosis type I, treated with CO_2 laser for four and a half years, as well as the results achieved.

CASE REPORT

A 37-year-old, single female patient originary from the Brazilian Northeast City of Aracaju (SE) referred dark spots on the body (six in number), from birth. At 23 years of age, she noticed the onset of lesions distributed throughout the integument. She denied family history of this pathology.

Physical examination allowed the observation of numerous papular and nodular cutaneous lesions, with diameters varying from 1.0 to 15.0 mm throughout the integument, mainly the face, neck, cervix and abdomen, and in smaller number in the limbs and dorsum. There was presence of brownish *café-au-lait* patches on the abdomen, chest, back and lower limbs.

Treatment started at the age of 26, when the patient underwent 23 surgical excisions, having had another 16 lesions removed later on. At the age of 37, 30 additional lesions were resected.

Treatment of lesions with CO_2 laser began at 37 years of age.

Procedure

Firstly, a test procedure was performed on three submandibular lesions. Two months after, good healing was observed, with absence of intercurrences and remission of the treated lesions. Thus, the treatment of the remaining lesions was started.

The Laser Pixel CO_2 70W, Alma Lasers (Halamish St. Caesarea Industrial Park, Israel) was used with the surgical tip, 2.5w, 10ms on-time, 20ms off-time. Lesions up to 3 mm in size were treated with the handpiece positioned perpendicularly to the surface, with circular movements. Larger lesions were initially cauterized at the periphery and then clamped at the base, with forced extrusion aiming at facilitating their delimitation. Surgical sutures were performed only in lesions larger than 1.0 cm. Post-cauterization curettage of lesions was carried out in the first sessions in order to confirm the complete ablation of the neurofibromas. On average, 50 to 100 lesions were treated per session, depending on their size. (Figure 1)

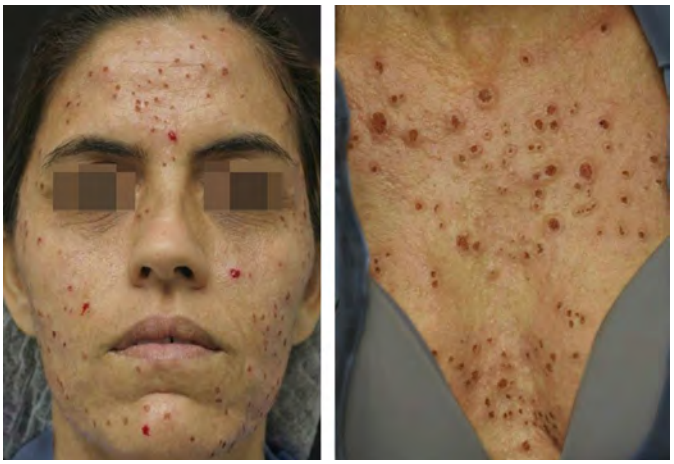


Figure 1: Pre and post-treatment (six sessions)

Sixteen sessions were carried out over four and a half years, with intervals varying from two weeks to ten months. A decision was made for treating a specific region's lesions per session, prioritizing the body sites of greater visibility (face, neck, neck, forearms, dorsum of the hands), and at a later stage later the chest, abdomen, arms and back. (Figures 2, 3 and 4)

Clinical development

Healing by second intention occurred in two or three weeks. There was no recurrence of the facial lesions; nevertheless there were recurrence of several lesions in the thorax, as well as in the abdominal region due to incomplete cauterization. The scars on the face and thorax remained erythematous for one to four months, developing into hypopigmentation and sometimes into atrophy. There were no additional complications.

DISCUSSION

The standard procedure for the removal of NF1 lesions is surgical excision, which has the advantage of leading to a linear scar. Disadvantages are longer procedure durations and greater risk of bleeding.[3-4] In light of this, CO_2 laser treatment is more suitable for the removal of large numbers of lesions with reasonable aesthetic outcomes and low risk of complications.[6-7]

Previous studies have shown that CO_2 laser treatment has improved the patients' self-confidence as well as their social and sexual lives. Algermissen *et al.* [4] reported that depigmented, laser treated scars were more acceptable to patients than scars resulting from surgical excisions, a finding that is in line with the opinion of the patients in the present study.

Table 1 shows a summary of the previously reported physical and psychological benefits of using CO_2 laser treatment.

The patient treated by the authors of the present report showed a high level of satisfaction, with hypopigmentation at

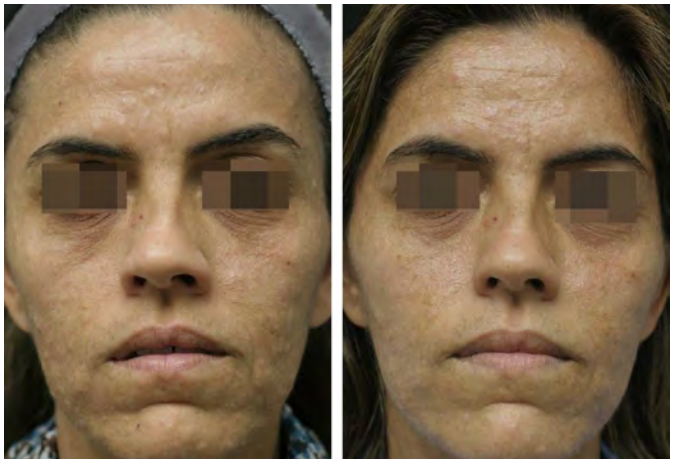


Figura 2: Pré-tratamento e pós-tratamento com seis sessões

Table 1: Summary of physical and psychological benefits

Studies	Main findings
Moreno *et al.*[5]	82% reported a good level of improvement in symptoms (e.g. pain, pruritus) and social activity
	73% reported a good level of improvement in sexual activity
	100% reported a good level of improvement in the feeling of *despair*
	satisfaction and recommendation rate = 73%
Algermissen *et al.*[4]	Most patients reported increased self-confidence and social acceptance
Chiang *et al.*	Satisfaction ate = 92%
	Recommendation rate = 100%

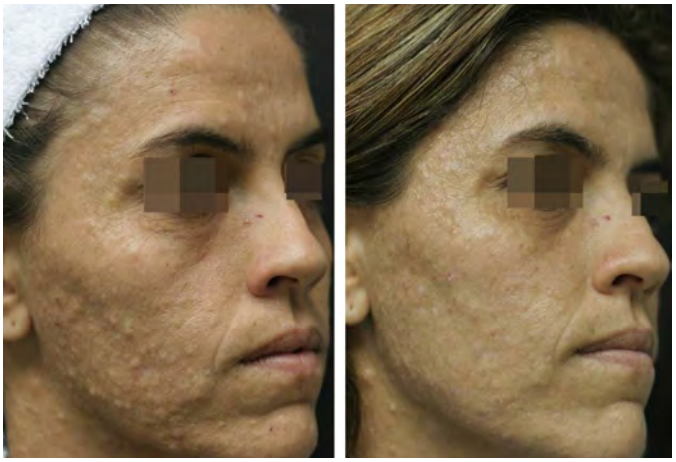


Figura 3: Pós-procedimento imediato de face e colo

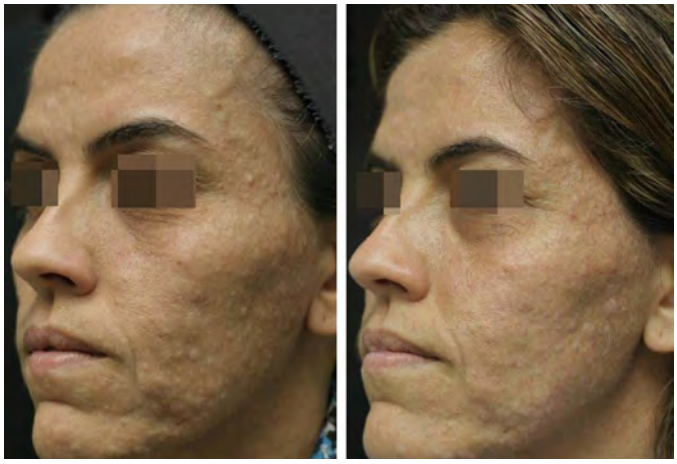


Figura 4: Pré-tratamento e pós-tratamento com três sessões

the treatment sites being the only adverse effect described, suggesting that the treatment with CO_2 laser has great potential in the improvement of the psychological well-being of patients suffering from this pathology. To date, no previous reports with long-term follow-up have been published, as was the case with the present paper.

CONCLUSION

Although there is no effective treatment to revert lesions characteristic of NF1, CO_2 laser is an option associated to a high level of patient satisfaction and swiftness in the approach of lesions, allowing to treat a large number of lesions per session, with a low risk of complications. ●

REFERENCES

1. Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. J Am Acad Dermatol. 2009;61(1):1-14.
2. National Institute of Health Concensus Development Conference. Conference statement. Neurofibromatosis. Arch Neurol, vol. 45, p. 575-8, 1988 https://www.ncbi.nlm.nih.gov/pubmed/3128965 https://jamanetwork.com/journals/jamaneurology/article-abstract/587659
3. Ferner RE. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. Lancet Neurol. 2007;6(4): 340-51.
4. Algermisse B, Muller U, Katalinic D, Berlien HP. CO2 laser treatment of neurofibromas o patients with neurofibromatosis type 1: five years experience. Med Laser Appl. 2001;16(4):265-74.
5. Moreno JC, Mathorest C, Lantieri L, Zeller J, Revuz J, Wolkenstein P. Carbon dioxide laser for removal of multiple cutaneous neurofibromas. Br J Dermatol. 2001;144(5):1096-8.
6. Steven M, Levine EL, Peter JT, HUBERT W. Electrosurgical excision technique for the treatment of multiple cutaneous lesions in neurofibromatosis type I. J Plast Recons Aesthet Surg. 2008;61(8):958-62.
7. Becker DW. Use of the carbon dioxide laser in treating multiple cutaneous neurofibromas. Ann Plast Surg.1991;26(6):582-6.

DECLARATION OF PARTICIPATION:

Luciane Prado Silva Tavares | ORCID 0000-0002-2410-3843
Approval of the final version of the manuscript, effective participation in the research guidance, intellectual participation in the propaedeutic and / or therapeutic conduct of the cases studied, critical review of the manuscript.

Osterno Potenciano | ORCID 0000-0002-7483-6463
Approval of the final version of the manuscript, effective participation research guidance, intellectual participation in propaedeutic and / or therapeutic approach of cases studied.

Yasmin Pugliesi | ORCID 0000-0003-0630-4980
Study design and planning, preparation and drafting of the manuscript, intellectual participation in the propaedeutic and / or therapeutic approach of the cases studied, critical review of the literature.

Raissa Lelitscewa da Bela Cruz Faria | ORCID 0000-0002-3925-9736
Preparation and drafting of the manuscript; data collection, analysis and interpretation; critical review of the literature.

Nathalia Lelitscewa da Bela Cruz Potenciano | ORCID 0000-0002-0002-8252
Preparation and drafting of the manuscript; data collection, analysis and interpretation; critical review of the literature.

Lara Silva Paixão | ORCID 0000-0001-7694-0531
Statistical analysis, preparation and drafting of the manuscript; data collection, analysis and interpretation; critical review of the literature.

Case Reports

Authors:
Helena Reich Camasmie[1]
Antonio Macedo D'Acri[1]

[1] Department of Dermatology, Dermatology Sector, Hospital Universitário Gaffrée & Guinle, Universidade Federal do Estado do Rio de Janeiro (UNIRIO) - Rio de Janeiro (RJ), Brazil.

Correspondence:
Helena Reich Camasmie
Rua Thales de Aquino Coelho, 160
Barra da Tijuca
22793-300 Rio de Janeiro, RJ
Brasil
Email: helena@camasmie.com

Received on: 13/01/2018
Approved on: 08/03/2019

This study was performed at the Department of Dermatology, Dermatology Sector, Hospital Universitário Gaffrée & Guinle, Universidade Federal do Estado do Rio de Janeiro (UNIRIO) - Rio de Janeiro (RJ), Brazil.

Financial support: None.
Conflict of interestss: None.

Milia on tattoo: successful conservative treatment

Mília sobre tatuagem: tratamento conservador bem-sucedido

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111135

ABSTRACT

Milia are keratin cysts of 1-3mm in diameter that occur due to the obstruction of eccrine sweat glands or hair follicles. We describe the case of a female patient with multiple white-yellow papules over a tattoo made six months prior to the consultation. Conservative treatment is an option, since there is the possibility of the lesion being transient and that it will spontaneously resolve. We opted for a conservative treatment with excellent final cosmetic outcome.

Keywords*:* Primary Treatment; Tattooing; Ink; Therapeutics

RESUMO

Mília são cistos de queratina de 1-3mm de diâmetro, que ocorrem devido à obstrução de glândulas sudoríparas écrinas ou de folículos pilosos. Descrevemos um caso em paciente feminina, com múltiplas pápulas branco-amareladas, distribuídas sobre uma tatuagem realizada seis meses antes da consulta médica. O tratamento conservador é uma opção, uma vez que há a possibilidade de que a lesão seja transitória e desapareça espontaneamente. Optamos por tratamento conservador com ótimo resultado estético final.

Palavras-Chave: *Tatuagem; Terapêutica; Tinta; Tratamento primário*

INTRODUCTION

Milia are keratin cysts that measure 1-3mm in diameter and occur due to obstruction of eccrine sweat glands or hair follicles. [1] The origin of these cysts is matter of debate and it has been suggested that they might originate from the inferior portion of the vellus hair's infundibulum, however their histogenesis remains uncertain. Visible on the face as multiple whitish papules, milia are usually treated by manual extraction. [2] They can be classified into primary, spontaneous and secondary, and might occur after minor trauma, use of topical or systemic drugs, and in association with inflammatory skin conditions. [1]

Considering the increasing number of people who decide to have tattoos on their skin, it is believed that this habit might pose a significant risk for the public health. The most frequent skin reactions to tattoos include allergic, infectious and granulomatous dermatoses. [3] The act of tattooing leads to damage of the cutaneous barrier, which may facilitate the hematogenous spread of several pathogens, since the needles reach the vessels of the dermis. Therefore, infections in the bloodstream may also occur. [4]

Tattoos are associated with increased risk of inflammatory conditions such as eczema, psoriasis and neoplasms. [5] The description of milia on tattoos is rare, with few cases having been described. In fact it is not clear whether the low frequency of this condition is due to the absence of reports or the low incidence of cases.

CASE REPORT

The authors of this paper describe a case of a female patient with multiple white-yellowish papules scattered over a tattoo performed six months before the medical appointment. The papules emerged approximately one month after the procedure, being clinically diagnosed as milia. The lesions were restricted to the tattooed area, mainly on the red pigment, but there were also some on the green pigment (Figure 1).

The authors of the present paper decided for adopting an expectant approach to the case. The lesions disappeared spontaneously after two years of follow-up (Figure 2).

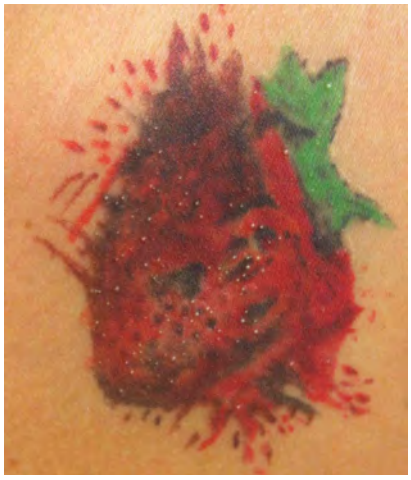


Figure 1: Small whitish papules confined to the tattooed area, mainly on the red pigment

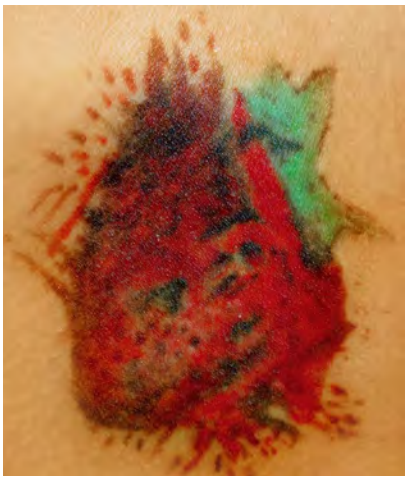


Figure 2: Regression of lesions after two years

DISCUSSION

Allergic reactions to red ink are the second most common complication after having a tattoo performed on the skin and occur due to the haptenization process that the red pigment undergoes. Although not exclusively, most of our patient's lesions were located over the region tattooed in red. Such lesions may occur at any time after the procedure and are generally asymptomatic.[3] The precise cause that could explain the emergence of milia after following tattooing procedures is not well explained in the literature and the authors of the present paper believe it is due to the trauma process and anomalous healing.

Conservative treatment is an option, since there is a possibility that the lesion may be transient and disappear spontaneously. Manual extraction with needles and dermabrasion are valid approaches, however can damage the original drawing.

CONCLUSION

The number of tattoos in the population is increasing significantly, and dermatologists should be aware of the possible complications as well as of the available therapeutic options. ●

REFERENCES

1. Avhad G, Ghate S, Dhurat R. Milia en plaque. Indian Dermatol Online J. 2014; 5(4):550-1.
2. Kurokawa I, Kakuno A, Tsubura A. Milia may originate from the outermost layers of the hair bulge of the outer root sheath: A case report. Oncol Lett. 2016;12(6):5190-2.
3. Ross N, Farber M, Sahu J. Eruptive Milia within a Tattoo: A Case Report and Review of the Literature. J Drugs Dermatol. 2017;16(6):621-4.
4. Dieckmann R, Boone I, Brockmann SO, Hammerl JA, Kolb-Mäurer A, Goebeler M, et al. Risk of bacterial infection after tattooing. Dtsch Arztebl Int. 2016;113(40):665-71.
5. Duan L, Kim S, Watsky K, Narayan D. Systemic allergic reaction to red tattoo ink requiring excision. Plast Reconst Surg Glob Open. 2016;4(11):e1111.

DECLARATION OF PARTICIPATION:

Helena Reich Camasmie | ORCID 0000-0003-0231-3003
Discussion and planning of the theme; data and bibliographic references analysis; drafting and final approval of the manuscript.

Antonio Macedo D'Acri | ORCID 0000-0002-2682-525X
Discussion and planning of the theme; data and bibliographic references analysis; drafting and final approval of the manuscript.

Letter

Authors:
Daniela Alves Pereira Antelo[1,2]

[1] Medical School, Universidade do Estado do Rio de Janeiro - Rio de Janeiro (RJ), Brazil.
[2] Cosmiatric Dermatology Sector, Hospital Universitário Pedro Ernesto - Rio de Janeiro (RJ), Brazil.

Correspondence:
Rua Visconde de Pirajá, 547 sala 901
Ipanema
22410-000, Rio de Janeiro, RJ
Brasil
Email: daniela@danielaantelo.com.br

Received on: 22/09/2018
Approved on: 22/12/2018

Financial support: None.
Conflict of interests: None.

The dark side of skin whitening

O lado negro dos clareadores cutâneos

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20191111258

ABSTRACT

This letter is a reflection that arose from the lecture given by Professor Fatimata Ly, from University Cheikh Diop in Dakar (Africa) in the latest Congress of the European Academy of Dermatology and Venereology in Paris. Professor F. Ly gave the lecture *"Depigmentation: when, where and how"*. An even skin tone is one of the criteria for beauty. This letter does not concern those patients that come to our practices and are carefully followed and monitored by discerning dermatologists. She wants to raise attention to those that do not come to our practices, that use prescriptions given to acquaintances, or that use a dermatologist prescription indefinitely, after a single consultation. I was recently part of "discussion" forums over the internet, anonymously, of lay people on melasma. The intensity and speed of sharing of what they recommend using are impressive. They are very creative suggesting the use of products that could cause harm. Among the most used lightening products are steroids, hydroquinone, mercury and acids. There must be an awareness campaign to warn the population regarding the dangers of using skin depigmenting agents without a specific indication by the dermatologist.

Keywords: Hyperpigmentation; Melanosis; Skin Care; Skin Pigmentation; hidroquinones

RESUMO

Esta carta traz uma reflexão surgida a partir da palestra da professora Fatimata Ly, da University Cheikh Diop de Dakar (África), no último Congresso da Academia Europeia de Dermatologia, em Paris. A professora F. Ly proferiu a palestra Depigmentation: when, where and how. O tom de pele uniforme é um dos critérios de beleza. Esta carta não diz respeito aos pacientes que chegam ao consultório médico e que são cuidadosamente acompanhados e monitorados por dermatologistas criteriosos. Ela quer chamar a atenção para os indivíduos que não chegam aos consultórios, que repetem prescrições de conhecidos ou que mantêm por tempo indefinido uma prescrição realizada por dermatologista numa consulta pontual. Recentemente, participei, de forma anônima, de fóruns de "discussão" na internet de pessoas leigas sobre melasma. A intensidade e a velocidade do compartilhamento em relação àquilo que eles aconselham são expressivas. A criatividade é enorme ao sugerirem usar produtos que podem causar algum dano. Entre os clareadores mais utilizados estão esteroides, hidroquinona, mercúrio e ácidos. Há que se realizar uma campanha de conscientização da população em relação aos perigos de se utilizarem despigmentantes cutâneos sem indicação precisa do médico dermatologista.

Palavras-Chave: *Hidroquinonas; Higiene da Pele; Hiperpigmentação; Melanose; Pigmentação da Pele*

I am writing to the Editorial Board of this Journal to share a reflection stimulated by the lecture given by Professor Fatimata Ly (Medical School of the University of Cheikh Diop, Dakar, Senegal), at the last Meeting of the European Academy of Dermatology that took place in Paris, in September of 2018. Professor Ly delivered the lecture "Depigmentation: when, where and how."

As dermatologists, we often prescribe the use of depigmenting agents to homogenize the skin's hue for the treatment

of aging or of the most varied hyperchromias caused by melasma, post-inflammatory hyperpigmentation, among others. The importance of this category of agents in our therapeutic armamentarium is indisputable, for a uniform skin tone is one of the criteria of beauty. On the other hand, the global market for whitening creams is expected to reach the magnitude of many billions of dollars (US$ 10 billion in 2015), with a clear economic interest to meet the demand for a fairer skin, which is idealized as synonymous with superior beauty. This market is expected to grow exceptionally up until 2027, in special in the Asian region. A methanalysis including 68 studies (67,655 participant patients) evidenced a prevalence of 27.7% of the use of cutaneous whitening agents.[1]

This letter does not concern patients who are treated at the physicians' practices, and are carefully monitored and followed up by discerning dermatologists. Conversely, it does not aim at drawing attention to individuals who do not attend dermatological appointments, but rather to those who rely on prescriptions given to acquaintances or use for an indefinite period a limited, condition-specific prescription given by a dermatologist. The application of intravenous glutathione, which is an antioxidant found naturally in human cells and has the ability to depigment the skin, is a reality in some countries of the globe. Each glutathione injection costs around US$ 150 – 400, with applications performed once or twice a week (10 to 30 sessions are recommended) at specialist practices, which are rapidly growing in number in Asia and Africa. In Asia, the Philipinne's FDA (Food and Drug Administration Agency) has banned the use of glutathione IV.

I have recently taken part – in an anonymous way – in "discussion" forums on the Internet with thousands of lay people who have melasma, witnessing the intensity and speed of their sharing what they advise, which are directly proportional to the negative impact on the quality of life caused by dyschromias. Huge is the creativity in suggesting products that can cause some type of harm.

Among the most popular whiteners used by used by people who do not have access to physicians are steroids, hydroquinone, mercury and acids. One study showed that depigmenters illegally sold in the European cosmetic markets contained hydroquinone and corticosteroids.[2]

Mercury, for instance, is found in some cosmetic soaps and creams. It is disposed of in rinsing water, which in turn is toxic to fish. There is a description of ingestion of contaminated fish by pregnant women, leading to neurological deficit in the fetuses.[3,4,5]

Although rare, some studies suggest the occurrence of squamous cell carcinoma in the skin that underwent depigmentation. Facial dermatitis may occur with the use of depigmenters: contact eczema and hypersensitivity reactions. These findings were observed in a multicenter study conducted in Dakar (Senegal), between March and September 2018, and that has been presented at the EADV 2018 Meeting by Prof. Ly (unpublished data). The onset of acne due to the use of corticosteroids is also described, in addition to the already largely known exogenous ochronosis, caused by hydroquinone.

It is necessary to carry out a campaign to raise public awareness regarding the dangers of using skin depigmenters without detailed indication from a dermatologist physician, who has all the scientific knowledge and legal support to prescribe the most suitable depigmenting agent and duration of use, according to each specific case. ●

REFERENCES

1. Sagoe D, Pallesen S, Dlova NC, Lartey M, Ezzedine K, Dadzie O. The global prevalence and correlates of skin bleaching: a meta-analysis and meta-regression analysis. Int J Dermatol. 2019;58(1):24-44.
2. Desmedt B, Courselle P, De Beer JO, Rogiers V, Grosber M, Deconinck E, et al. Overview of skin whitening agents with an insight into the illegal cosmetic market in Europe. J Eur Acad Dermatol Venereol. 2016;30(6):943-50.
3. Ori MR, Larsen JB, Shirazi FM. Mercury Poisoning in a Toddler from Home Contamination due to Skin-Lightening Cream. J Pediatr. 2018;196:314-317.
4. Mohammed T, Mohammed E, Bascombe S. The evaluation of total mercury and arsenic in skin bleaching creams commonly used in Trinidad and Tobago and their potential risk to the people of the Caribbean. J Public Health Res. 2017;6(3):1097.
5. Ho YB, Abdullah NH, Hamsan H, Tan ESS. Mercury contamination in facial skin lightening creams and its health risks to user. Regul Toxicol Pharmacol. 2017;88:72-76.

DECLARATION OF PARTICIPATION:

Daniela Alves Pereira Antelo | ORCID 0000-0001-8203-1772
Study design, literature review and manuscript drafting.

Surgical & Cosmetic Dermatology

January / February / March 2019

Print in March 2019