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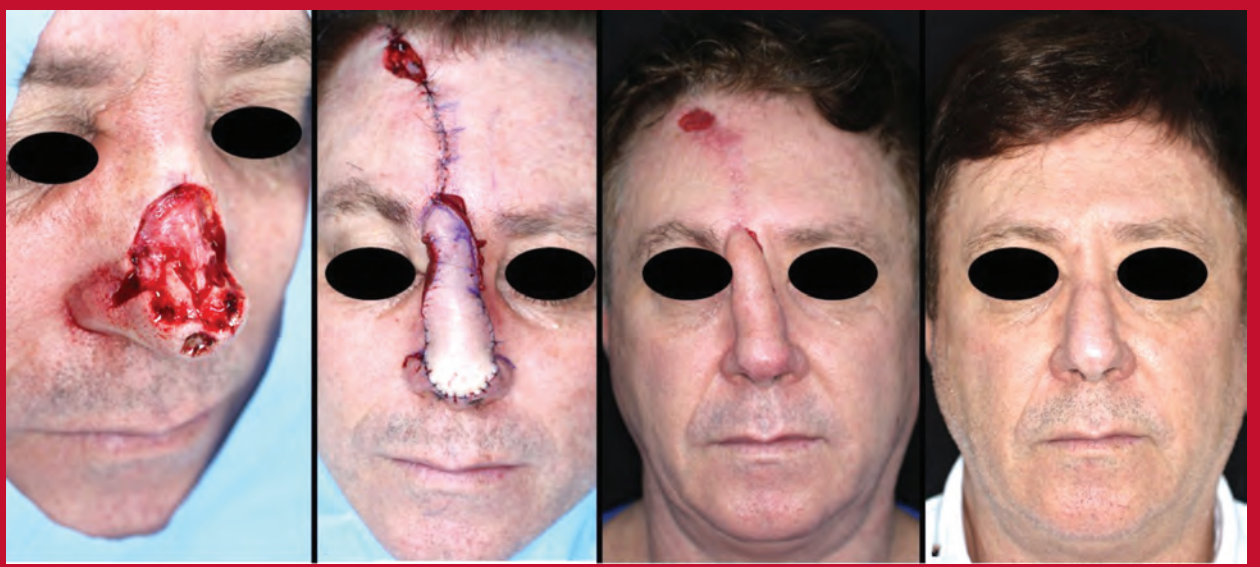
Nasal reconstruction after Mohs micrographic surgery: analysis of 208 cases



Role of upper blepharoplasty in facial rejuvenation

Treatment of median sternotomy scars using Triamcinolone injections, Silicone Dressings and a combination group: a prospective 34 randomized comparative study

Comments on sequential Jessner's + 35% TCA peel for the treatment of facial field cancerization

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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.

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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 (ICMJE), (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). A inclusão em um registro público de ensaios clínicos é uma condição para a publicação de ensaios clínicos nesta revista, de acordo com as recomendações do ICMJE.

Serão produzidos exemplares impressos da versão em língua portuguesa, com resumos e títulos em inglês. A versão completa em lingua está 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*).

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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

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A revista S&CD procura manter suas normas em constante atualização, caminhando em conjunto com as tendências da publicação científica. Aceitamos os Preprints como forma de incentivo à comunicação entre os autores e para dar agilidade à ciência.

Preprint é um manuscrito científico previamente depositado pelos autores em repositórios, afim de disseminar os dados de pesquisa mais rapidamente. Depositar um manuscrito em plataforma de Preprints não é considerado publicação duplicada. No entanto, a S&CD não aceita manuscritos já publicados anteriormente em outro periódico.

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 quando aprovado, o autor correspondente será comunicado sobre a aprovação e depois sobre a publicação, também receberá uma prova final para aprovação e correções.

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

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Contato da revista:

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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 estatisticas, podendo ser incluidas notas tecnicas dos autores. 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.org)

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 45 referências e seguir o formato IMRDC (Introdução e objetivo, Métodos, Re-

sultados, 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, relato de caso, 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

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The effects of estrogens and phytoestrogens on human skin and its topical use for prevention of skin aging - Literature Review

Os efeitos dos estrogênios e fitoestrogênios na pele humana e seu uso tópico para prevenção do envelhecimento cutâneo: revisão da literatura

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20201211397

ABSTRACT

Skin quality and function drastically reduces with age due to chronological aging, photoaging, environmental factors and hormonal deficiencies. Decreased menopausal estrogen levels play a role in cutaneous atrophy, collagen and water content, loss of elasticity, skin wrinkling and deficiency of wound healing. Much research has been done to elucidate the beneficial effects of topical estrogen, which would have a more localized action on the skin without systemic side effects. The objective of this study was to review the relevant literature, demonstrating that this may be a safe and effective alternative for the treatment of women's skin in perimenopause.

Keywords: *Estrogens; Phytoestrogens; Skin aging; Collagen; Antioxidants*

RESUMO

A qualidade e a função da pele reduzem-se drasticamente com a idade devido ao envelhecimento cronológico, ao fotoenvelhecimento, aos fatores ambientais e às deficiências hormonais. O declínio dos níveis de estrógeno na menopausa tem papel importante na atrofia cutânea, redução do colágeno, perda de elasticidade e deficiência da cicatrização de feridas. Pesquisas têm demonstrado os efeitos benéficos do estrogênio tópico, que teria ação mais localizada na pele sem efeitos colaterais sistêmicos. O objetivo deste estudo foi revisar a literatura pertinente ao assunto, demonstrando que o uso do estrogênio tópico pode ser uma alternativa segura e eficaz para o tratamento da pele de mulheres na perimenopausa.

Palavras-Chave: Antioxidantes; Colágeno; Estrogênios; Envelhecimento da pele; Fitoestrógenos

Review

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INTRODUCTION

Life expectancy for women has increased significantly in the past century. In the United States, it was approximately 50 years in 1900, and currently, it exceeds 80 years.[1] In Brazil, according to the Instituto Brasileiro de Geografia e Estatística (IBGE), in 1940, the life expectancy was 48.3 years, and, in 2015, it reached 79.1 years.[2] Thus, today, women are expected to spend more than a third of their lives after menopause, which leads to greater concern about health care in this period.[3]

The quality of the skin deteriorates with age due to chronological aging, photoaging, environmental factors, and hormonal deficiencies. Menopause is a milestone in a woman's life, which is accompanied by a significant drop in hormone levels. This change causes numerous symptoms that constitute the climacteric, among them the accelerated decline in skin conditions. The drop in estrogen levels that occurs in this period plays an essential role in cutaneous atrophy, in the collagen and water content reduction, in sebaceous secretions decrease, in elasticity loss, and in skin wrinkling, as well as in the wound healing deficiency.[4]

Consequently, it is vital to carefully study the molecular effects of estrogen on the skin and its corresponding cutaneous manifestations.

The critical role of estrogen in skin integrity has been demonstrated with the discovery of estrogen receptors in dermal fibroblasts and epidermal keratinocytes.[4,5,6,7] Studies have shown that 17 [b]-estradiol and genistein can combat skin aging through its protective effects related to modulating lipid peroxidation, as demonstrated in dermal fibroblasts extracted from patients with Friedreich's ataxia.[8] They also act on the mitochondrial membrane potential through mechanisms related to estrogen receptors (classical and non-classical) and the activation of kinases.[5,6] Thus, estrogen can exert its physiological effects through a combination of genomic and non-genomic pathways.[9]

The use of estrogens has shown beneficial effects in the prevention and repair of skin aging in postmenopausal women. The acceleration of skin aging observed in women during the climacteric evidences its importance in maintaining human skin homeostasis.[8,9] In general, estrogens not only improve collagen content and quality but also increase dermal thickness and vascularity. Also, they contribute to enhancing the migration of keratinocytes and, consequently, accelerate the wound healing process.[7] Phytoestrogens also represent promising alternatives for the treatment of skin aging, especially genistein, which has antiphotocarcinogenic and antiphotoaging properties by modulating the oxidant/ antioxidant balance.[5]

In recent years, much research has been conducted to elucidate the effects of topical estrogen, which would have a more localized action on the skin without the adverse events of systemic hormone replacement. Thus, topical estrogen can be a safe and effective alternative for skin treatment of women in perimenopause.

OBJECTIVES

Review national and international scientific publications, through a narrative review of the literature, to assess the role of topical estrogens and phytoestrogens in human skin and their effect on skin rejuvenation.

METHODS

This is a narrative review of the literature of articles published in journals in Portuguese and English between 1993 and 2018. A bibliographic search was conducted from July to November 2018 using the search engines in the electronic resources of the following databases: Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Health Information from the National Library of Medicine (Medline), Web of Science, Scopus, and in the electronic library Scientific Electronic Library Online (SciELO).

The descriptors (DeCS) used were: estrogênios/es- trogens, fitoestrógenos/phytoestrogens, envelhecimento da pele/ skin aging, colágeno/collagen, antioxidantes/antioxidants.

Additionally, a detailed manual search of the references of the selected articles was performed to find studies not identified in the online search.

RESULTS

After identifying the articles in the mentioned search sources, we selected: clinical studies with women in perimenopause treated with topical estrogen or phytoestrogen; literature reviews on the effects of topical estrogen on human skin and skin aging; clinical studies with histological cuts and cultures of human cells and the effects of estrogens in vitro; and clinical studies with evaluation of the effects of estrogens and phytoestrogens on the skin of animals and the molecular mechanisms of the action of this hormone. Clinical studies with systemic hormone replacement and case reports were excluded. In total, we included 16 clinical studies and eight literature reviews.

DISCUSSION

Human skin is composed of a connective tissue highly rich in collagen, which provides essential structural, and functional support. Type I (80%) and type III (15%) collagens are prevalent.[9] In the aging process, the dermal collagen fibers decrease in number and fragment, thinning and weakening the skin structure. These changes in collagen fibers create a microenvironment that promotes age-related skin diseases.[10,11,12] In women, a significant drop in hormone levels that occurs in climacteric and menopause accompanies chronological aging. These changes cause numerous symptoms, among them, the accelerated decline of skin conditions.

As interest in skincare after menopause is increasing, studies on the beneficial effects of estrogens and phytoestrogens on the aging skin have also been significantly expanding.

According to Shu et al.,[9] there are two predominant forms of estrogen receptors in the skin, called estrogen receptor a (ER α) and estrogen receptor Symbol (ER β).[9,13,14]

These receptors are distinct proteins encoded by different

genes; [15] however, both bind to estradiol with similar affinity. Thus, estrogen acts through two distinct mechanisms: the classic pathway, with estrogen receptors ERα and ERβ, involving the nuclear localization of the hormone-receptor complex, which alters the expression of target genes; and the non-classical pathway, which initiates a rapid cascade of intracellular signaling by coupling the hormone to estrogenic receptors on the cell membrane, including the G protein-coupled estrogen receptor (GPER or GPR30).

The molecular basis of the estrogen action on the skin has been gradually elucidated in recent studies. In 2018, Savoia et al.[5] demonstrated in their research a protective effect of genistein and 17 β-estradiol against peroxidative damage in fibroblasts and keratinocytes by modulating the release of nitric oxide (NO) and reactive oxygen species (ROS), glutathione content (GSH) and mitochondrial function. The involvement of estrogen receptors (ERs), non-classical membrane G protein-related estrogen receptor (GPER30), and kinase activator (PI3K-Akt, p38 MAPK, ERK ½) has also been elucidated. Furthermore, it has been shown that estrogens induce remodeling of the actin cytoskeleton in isolated human dermal fibroblasts through the ER-independent, GPER30-dependent non-genomic mechanism.

Carnesecchi et al.[6] showed that the lack of estrogens induces rapid reorganization of the cytoskeleton of human dermal fibroblasts, resulting in a significant change in the cell format. After the replacement of 17 β-estradiol, the cell morphology, and organization of the cytoskeleton were completely restored. The receiver involved would be the non-classic GPER-30. Richardson et al.[8] demonstrated potent cytoprotective properties of estrogens in vitro. They can prevent lipid peroxidation and the collapse of mitochondrial membrane potential, increase oxidative phosphorylation, and maintain ATP levels and aconitase activity in fibroblasts in patients with Friedreich's ataxia (FRDA).

Another study, by Zhou et al.,[7] observed that estrogen accelerates wound healing by inducing proliferation of epidermal keratinocytes via the intracellular Erk/Akt signaling pathway, both in vitro and in vivo. Phytoestrogens are substances produced by plants, with structural and functional properties similar to those of estrogens. There are three main classes: isoflavones, lignans, and coumestans.[16] Among them, isoflavones, especially genistein, are the best studied. These bind directly to estrogen receptors, exerting both agonist and antagonist effects.[17,18] Several studies have shown that isoflavones promote beneficial effects on aging skin in terms of photoprotection, elasticity, hydration, and wrinkle prevention.[10] A study by Cicrosta et al.,[19] published in 2006, with ovariectomized rats, conducted oral treatment with isoflavones (20 and 40 mg/day for 14 weeks). The results presented general improvement in skin morphology and a significant increase in skin collagen in the treated group compared to the control group. Therefore, phytoestrogens have been considered as potential alternatives to estrogen.

However, long-term hormone replacement therapy has been associated with unwanted systemic effects. Thus, in the search for safe and effective alternatives, the most localized effects on the skin of topical estrogens and phytoestrogens have been explored.

In 1996, Schmidt et al.[10] compared the effects of estradiol cream 0.01% and estriol 0.3% in 59 patients in the peri and post-climacteric with signs of skin aging and who did not undergo hormone replacement. After six months, a significant improvement in skin aging symptoms was observed. Both estriol and estradiol, at the concentrations used, demonstrated comparable results. Fewer adverse events have been reported in the estriol group. Ten patients were biopsied, and there was a significant increase in type III collagen.[10]

In a randomized, double-blind study with 30 patients between 45 and 55 years old, Silva et al. [20] compared the effects of using topical estrogen and topical genistein on the skin collagen of postmenopausal women. The patients were divided into three groups: topical estradiol, topical genistein, and control. There was a statistically significant increase in both type I and type III collagen in the groups that used estradiol and genistein. The possibility of systemic absorption of topical estrogen was also a variable studied, with vaginal smears and transvaginal ultrasound performed to measure the thickness of the endometrium before and after treatment. Furthermore, serum estradiol was measured before and 24 weeks after the therapy. Initially, all selected women had vaginal and endometrial atrophy, with serum estradiol levels below 20 pg/ml. None of these parameters changed after the treatment. Based on these results, it can be inferred that topical therapy with estrogen and genistein doesn't cause significant systemic adverse events.

Genistein has a molecular structure very similar to that of estradiol, presenting significant effects on the skin due to its ease in binding to estrogen receptors[21,22] and it has been shown to provide protective effects against photoaging and photocarcinogenesis in human and animal skin when applied topically.[23,24] A double-blind, randomized study by Moraes et al.[25] (2009), applied topical genistein gel 4% to the facial skin of postmenopausal women for 24 weeks, with improved dermal vascularization and increased epidermal thickness. Patriarch et al.[26] demonstrated an increase in the concentration of hyaluronic acid and fibroblasts in the dermis after topical treatment with genistein and estrogen. Thus, phytoestrogens are also promising alternatives in the treatment of skin aging.

CONCLUSION

The drop in serum estrogen levels in climacteric and menopause contributes significantly to the decline in skin functions. In turn, hormone replacement with estrogen or phytoestrogens favorably influences the quality of the skin and its functions in several aspects, promoting anti-aging action due to its ability to prevent the decrease in collagen concentration, restores skin elasticity, and increase skin hydration, in addition to the essential role in improving wound healing. However, despite the numerous positive effects of estrogen on the skin, systemic hormone replacement should not be considered solely to combat skin aging.

On the other hand, studies show that topical treatment with estrogens or phytoestrogens, especially genistein, also im-

proves the quality of the skin and does not significantly increase the systemic dosage of these hormones. Thus, topical estrogenic compounds represent a new, promising, and safe therapeutic approach for skin aging in women in perimenopause. ●

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Review Article

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Role of upper blepharoplasty in facial rejuvenation

Função da blefaroplastia superior no rejuvenescimento facial

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ABSTRACT

It is noteworthy the range of facial treatments, with aesthetic purpose, with which we can preserve the balance of the shape or beauty of our patients. Fillers, botulinum toxin, laser, and other technologies are widely used in dermatology. Eyelids can also be treated with these and other therapeutic resources. However, herniation of the fat pockets of the upper eyelids does not present significant results with these methods. The advancement of techniques known as minimally invasive and other technologies does not satisfy the treatment of this facial aesthetic unit. Thinking about the global rejuvenation of the face, it is unlikely that we will achieve a result of excellence without acting on the eyelids. Upper blepharoplasty remains irreplaceable, and it is the treatment of choice for skin redundancy and herniation of fat pockets. This surgery, with a long history in Dermatology, has a unique and fundamental role in facial rejuvenation. In this study, we tried to demonstrate the surgical technique of superior blepharoplasty educationally and to prove its efficacy and safety, with good aesthetic and functional results. With full knowledge of this anatomical region and technical precepts, we recognize that we can perform it safely.
Keywords*: Blepharoplasty; Surgery, plastic; Eyelids; Esthetics; Dermatologic surgical procedures; Rejuvenation*

RESUMO

Notável é a gama de tratamentos faciais, com intuito estético, com os quais podemos preservar o equilíbrio da forma ou a beleza de nossos pacientes. Preenchimentos, toxina botulínica, laser e outras tecnologias são amplamente demonstrados à classe dermatológica. As pálpebras também podem ser tratadas com esses e outros recursos terapêuticos. No entanto, a herniação das bolsas de gordura das pálpebras superiores não tem resultados significativos com esses métodos. O avanço das técnicas conhecidas como minimamente invasivas e das tecnologias não supre a contento o tratamento desta unidade estética facial. Pensando no rejuvenescimento global da face é improvável conseguirmos um resultado de excelência sem atuar nas pálpebras. A blefaroplastia superior segue insubstituível e é o tratamento de escolha para redundância da pele e herniação das bolsas de gordura. Esta cirurgia, com amplo histórico na Dermatologia, tem um papel único e fundamental no rejuvenescimento facial. Procuramos neste estudo demonstrar a técnica cirúrgica de blefaroplastia superior de maneira didática e comprovar sua eficácia e segurança, com bons resultados estéticos e funcionais. Com pleno conhecimento desta região anatômica e dos preceitos técnicos, reconhecemos poder realizá-la com segurança
Palavras-Chave: Blefaroplastia superior; Cirurgia cosmética; Pálpebras/cirurgia; Estética; Procedimentos cirúrgicos dermatológicos; Rejuvenescimento

INTRODUCTION

Cosmetic Dermatology has witnessed rapid progress in recent years with the use of minimally invasive procedures such as facial fillers, application of botulinum toxin, laser, and other technologies, Dermatology has achieved satisfactory levels of facial rejuvenation. Meanwhile, the upper eyelid is an aesthetic unit that has not enjoyed significant results, even when considering this technical progress and the possibility of using various technologies. A surgical approach is thus required. When addressing the aging process in the periorbital region, one should take into account the eyelid's skin quality and the effect from herniation of the fat pads.[1-4]

There is currently no procedure or technology that efficiently corrects these periorbital alterations with results as good or better than upper blepharoplasty. This shows the need for the dermatologist's command of the blepharoplasty surgical technique in order to solve problems and provide satisfactory overall facial rejuvenation.

OBJECTIVE

Review the knowledge of the anatomy involved in upper blepharoplasty, describe the surgical technique didactically, and prove its efficacy and safety, with good aesthetic and functional results.

BACKGROUND

Reports of surgeries to remove skin from the upper eyelids date back more than two thousand years. In the 19th century, such removal was for cosmetic purposes. Mackenzie and Dupuytren were among the first to describe the technique. After nearly 100 years, Miller optimized the technique and described it again.5 Graef was the first to use the term blepharoplasty in 1818 for treatment of a skin cancer of the eyelid, as a procedure commonly performed by dermatologists and an example of cosmetic surgery originating from oncological surgery. French dermatologist Susanne Noll was one of the pioneers in cosmetic blepharoplasty and facelift surgery, contributing major advancements to cosmetic dermatological surgery.[5]

Castanares, Fournier, and González have recently contributed to the technique's advancement.[5]

ANATOMY

The key to surgery of the eyelids and the periorbital area is in-depth knowledge of this complex region's anatomy. The dermatologist must know the anatomy in detail, since the area to be corrected by surgery is as important as those that may be affected by unintended manipulation of various structures in this surgical field.

The eyelids are mobile folds covered externally by thin skin and internally by the lid's tunica conjunctiva. The upper and lower eyelids are reinforced by dense bands of connective tissue, the upper and lower tarsi, which form the eyelids' "skeleton".[6]

The eyelid's skin and a thin layer of subcutaneous tissue lie on the orbicularis oculi muscle. The palpebral portion of the orbicularis oculi is divided into two portions: pretarsal and preseptal.

The pretarsal portion is situated on the tarsal plate of the orbicularis oculi and is attached firmly to it. It begins at the lateral canthus and is inserted into the medial canthus. The superficial portion forms the anterior part of the medial canthus tendon, and the deep portion is inserted into the bone of the lacrimal crest, forming the posterior tendon of the medial canthus. When contracting, the eyelid closes by approaching the lacrimal point of the lacrimal sac.[7-8]

The preseptal portion attaches loosely to the skin. It covers the orbital septum of the upper and lower eyelids, and its fibers join laterally to form the lateral palpebral raphe. The preseptal portion inserts into the lacrimal fascia on the lateral portion of the lacrimal sac, and on contraction, it allows tears to enter the lacrimal sac. When the muscles relax, the lacrimal fascia returns to its normal position, and the tears flow directly into the nasolacrimal duct. [8-9]

Located at the junction of these two portions is the supratarsal crease, which is important to identify in eyelid surgery.

The levator palpebrae superioris muscle, the four rectus muscles (superior, inferior, lateral, and medial), and the two oblique muscles (superior and inferior) are the principal extraocular muscles.[10]

Immediately below the orbicularis oculi muscle is the orbital septum, a fibrous membrane of connective tissue that separates the orbital fat pads and deep orbital structures from the eyelid itself, and that performs containment of the orbital fat tissue and other orbital structures. The fat pad compartments lie behind the septum. With aging, both the septum and the orbicularis muscle and the skin become more saggy and thinner, leading the orbital fat to prolapse, making it more prominent and ptotic.[8]

These fat pads are surrounded by a thin fibrous fascia, individualizing them in compartments.

The upper eyelid has two compartments, central and nasal.[11, 12] The central fat pad is situated anteriorly to the aponeurosis of the levator palpebrae, with a golden hue (Figure 1). The nasal fat pad is whitish-yellow in color and can be identified during blepharoplasty by exerting soft pressure on the eyeball and delicate divulsion of the nasal septum. Between the nasal and central fat pad lies a minimal but clear accumulation of adipose tissue that mimics separating the two pads and is associated loosely with the pre-aponeurotic pad; this structure is known as the adipose tissue transition. The trochlear and supraorbital branches of the superior ophthalmic vein are situated under it. Bleeding from this vein should be cauterized under direct visualization, because blind deep electrocauterization can injure the trochlea (or pulley of the superior oblique muscle) and cause diplopia.[13-14]

The lacrimal gland is arranged laterally. It can be confused with the fat pads, and care must be taken not to injure it inadvertently during surgery. The arterial supply to the eyelids and the venous drainage must also be observed and maintained intact during eyelid surgery.

The tarsi are structural elements of the eyelids consis-

ting of dense fibrous tissue approximately 29mm wide and 10 to 12mm high at the midpoint, and 1mm thick. The inferior tarsus has the same width and thickness and is 5 to 6mm high. The tarsi begin medially at the lacrimal point and extend to the lateral commissures. Embedded vertically in the tarsal laminae and extending to their marginal aspects are the Meibomian sebaceous glands. There are 34 glands in the upper eyelids and 20 to 30 in the lower lids.[12]

TECHNIQUE

Patient selection should involve the analysis of several factors, listed in Chart 1.

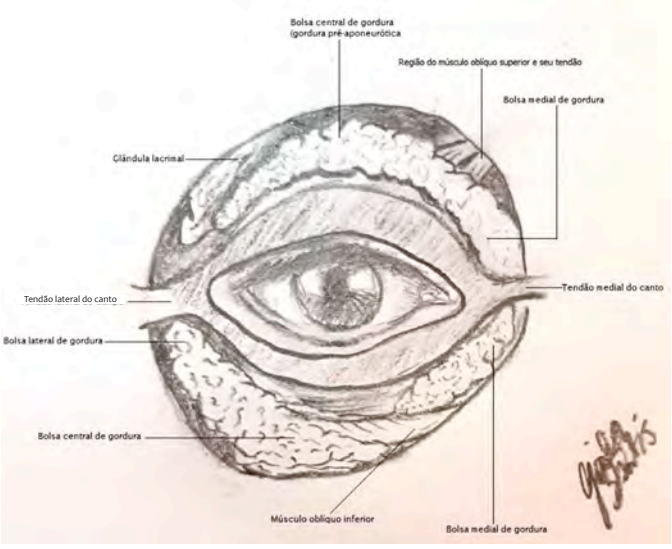

FIGURE 1: Anatomy of the palpebral region

CHART 1: Factors analyzed in patient selection

1. Anatomical factor: Is there redundant skin? Is there probably redundant fat? Are both structures redundant?

2. Can the case be corrected with blepharoplasty or should one consider the hypothesis of a brow lift, temporo-frontal filling, or even relaxation of the region's depressor muscles with secondary augmentation of the frontal muscle's contraction with botulinum toxin?

3. Psychological factor: is the patient prepared, and does he or she have realistic expectations?

4. Are there contraindications to surgery? Are they absolute or relative?

5. Analysis of the eyelids: Have the side effects and asymmetries been discussed with the patient? Perfect symmetry does not exist either before or after surgery.

6. Has the patient undergone previous procedures on the eyelids (laser, phenol peeling, or even blepharoplasty)? This should be recorded in writing on the chart, with photos, especially when there is scleral show.

7. What is the height of the eyebrows? The eyelids bear a close relationship to the eyebrows, and when the latter are low, especially in men, care must be taken when removing excess skin. It is also important to remove less than possible in order to avoid overcorrection, with sunken eyes.

PREOPERATIVE ASPECTS

At least two consultations are necessary before the surgery. For dermatologists, in most cases several consultations and procedures have been performed prior to blepharoplasty. This prior interpersonal relationship with patients facilitates the preoperative preparation.

Preoperative preparation includes assessments of overall health status, history of medications, personal and family history of wound healing, and allergies, that is, a detailed patient work-up.

It is necessary to explain and furnish in writing the pre-, inter-, and postoperative care, probable recovery time, possibility of side effects such as dry eye, hematoma, and edema, among others, and possible surgical complications. In case of doubt as to the preexistence of dry eye, the Schirmer test should be performed. It should also be explained to the patient that a possible ptosis of tear glands will not be resolved by this surgery.

Prophylactic antibiotic therapy is performed with 2g of cephalexin 30 to 60 minutes before surgery. If the surgery is performed with local anesthesia, fasting is not necessary. The anxiolytic lorazepam 1 to 2mg can be administered on the night prior to the procedure and after breakfast on the day of the surgery.

Photographic documentation is mandatory, as in all cosmetic procedures. The entire face should be documented, from the chin to the hairline, with the eyes open and closed, from the three angles (front, side, and oblique). Detailed photographs should also be taken of the orbital region, focusing on wrinkles, asymmetries, and scleral show.

The informed consent term, explaining possible complications of the surgery, should be signed to leave no doubts in the patient's mind.

Preoperative tests include: complete blood count, TSH, free T4, blood glucose, liver enzymes, renal function, PT, and aP TT.

Anatomical nomenclature: (Figure 2)

- Skin: preseptal or supratarsal palpebral crease.
- Supratarsal crease.
- Orbicular muscle, preseptal portion is 3 or 4mm above the superior border of the tarsus.
- Fibrous orbital septum: courses from the orbital crease to the marginal arch (formed by the levator aponeurosis), which originates as a muscle, becomes fibrous, and inserts into the anterior base of the tarsus. The Müller muscle is located in its posterior portion.
- In Caucasians, the insertion is in the superior part of the tarsus; in Asians, the insertion is lower, and thus it does not form the supratarsal crease.
- Tarsus.
- Pre-aponeurotic medial or central fat pads.
- Nasal or medial pad – inferior to tendon of the superior oblique muscle – lighter in color and more fibrous and denser.

Incisions: defat the skin with chlorhexidine-alcohol for better fixation of the marking ink. Marking performed with the patient in sitting position.

First marking is on the supratarsal crease, well-defined in Caucasians and poorly defined or absent in Asians.

1st marking; demarcate the supratarsal crease (Figure 3a).

The distance between the supratarsal crease and the ciliary border varies from 6 to 8mm when measured at the mid--pupillary line.

As for the extremes of the incision, at the nasal canthus the scar should respect the palpebral aesthetic unit, not invading the lateral wall of the nose due to the risk of cicatricial bands and adhesions (fibrotic band of the medial canthus).

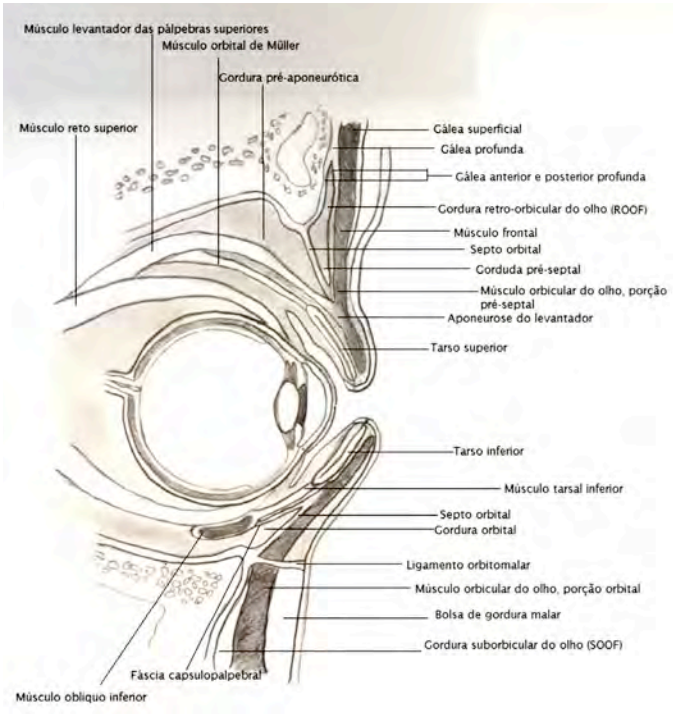

Figure 2: Anatomy of the ocular region

The aesthetic unit is more accommodating at the scar's lateral canthus and can be extended, which improves the skin's accommodation when necessary.

If not necessary, the scar can remain within the eyelid's aesthetic unit. If it is necessary to prolong the incision, it should be kept within a natural crease or wrinkle of the skin. A lateral prolongation of the supratarsal crease is created.

The definition of the superior incision line is based on clinical assessment. This is where the state of the art comes into play in blepharoplasty. A combination of sensitivity and theory determine the site for this incision line.

The mid-pupillary line is marked.

One then identifies the highest point: the apex of the incision line will be located at this point (Figure 3b). Some characteristics dictate this point: the end of the palpebral elastosis when examining from inferior to superior. From the supratarsal crease onward, the skin is more damaged.

When the skin presents its natural characteristics again, the excision plane is finalized. Not all the cases will present this morphological difference which helps us in marking the upper limit of the area to excised, and in these cases, in which the limit between the elastotic skin and the healthy skin is not clear, the superior marking line should be made using the pinch test with an anatomical clamp or pachymeter, as shown in Figure 4a, joining the two extremities and thus preserving the palpebral rim, if that portion of the skin is needed for good closure of the palpebral rim.

Measurement of the distance between the supratarsal crease and the upper line of the surgical plane is essential for bilateral comparison, although 1mm or slightly more may exist as the difference between the two eyelids.

Tracing of the incision lines should always observe two factors: the natural closure of the palpebral rim, and that the incisions remain within the natural lines and thus be disguised when the eyes are open.

The pinch test of the entire region, from lateral to central, should be verified. Patients should open and close their eyes

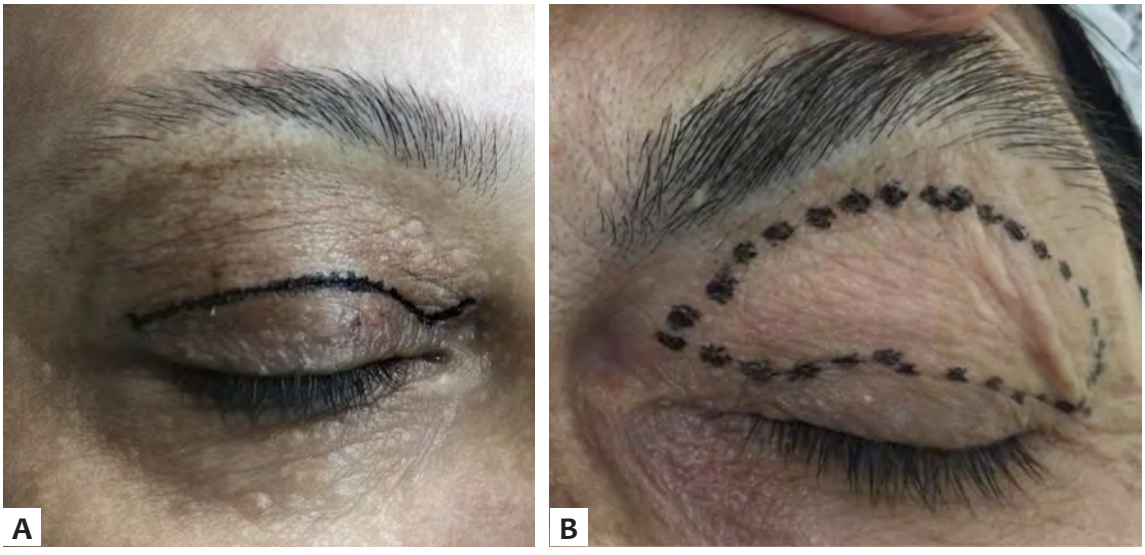

Figure 3: A. Marking of the incision line on the supratarsal crease. **B.** Marking of the incision, with upper, lower, lateral and medial limits and skin with elastosis.

on command to perform this test.

The greatest risk and main cause of insecurity in one's first surgeries of the upper eyelid is the removal of excessive skin,, leading to non-closure of the palpebral rim.

On the medial border, the risk involves formation of fibrous cicatricial bands.

On the lateral border, it is important to observe the distance between the superior ciliary border or the angle formed between the upper and lower lateral eyelids and the inferior incision line (supratarsal). A distance of less than 4mm can compromise the lymphatic drainage and cause chronic lymphedema of the upper eyelid.5 Figure 4c illustrates the minimum permissible limit between the lateral canthi and the incision line.

The lateral and medial extremities should allow access to the preseptal palpebral crease.

Another important factor for marking the superior incision line in the surgical plane is the relationship between the eyelid and eyebrow. Individuals with low eyebrows (the pattern seen in men) should not have a superior incision line very far from the supratarsal line. That is the distance between the mid--pupillary points and the supratarsal incision line and superior line should be sparing enough not to remove too much skin and lead to sunken eyes. The shadow formed by the eyebrow after removal of the skin will give the sensation of proximity between the eyebrow and ciliary border, producing a "sunken eye" appearance.

SURGERY

Patient in supine position.

Monitored (heart rate, arterial pressure, and oxygen saturation).

Surgeons' preparation according to protocol, washing hands, drying, donning sterile gown and sterile gloves.

Antisepsis with aqueous chlorhexidine to avoid removing previous marking of the surgical plane.

Placement of sterile surgical drapes.

Preparation of anesthetic and cooling solutions (Chart 2) and delicate surgical instruments (Chart 3).

It is essential to test the Kelly forceps' grasping capacity with a folded gauze.

Anesthetize the lateral canthus and proceed to the medial canthus.

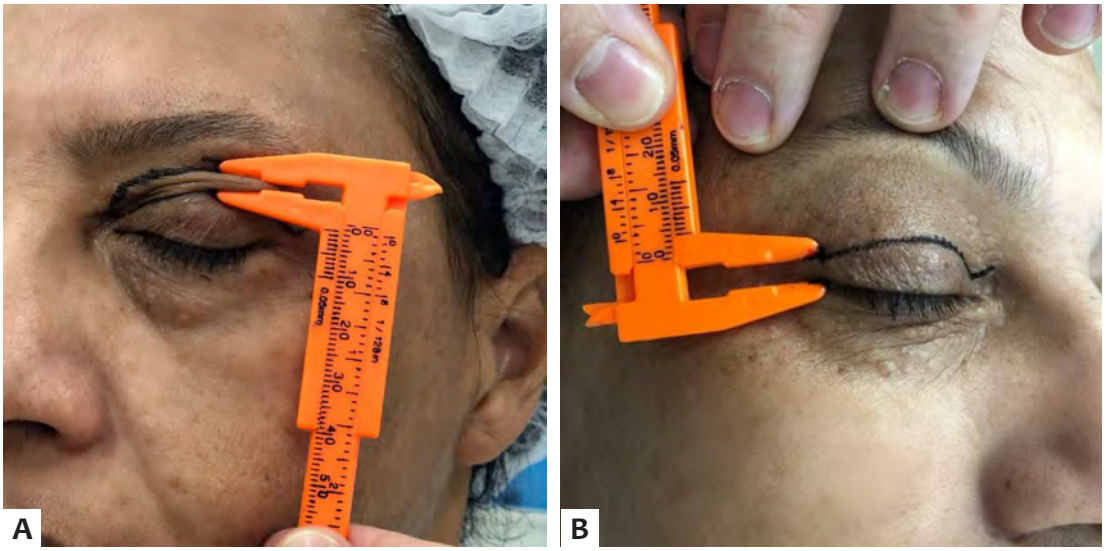

Figure 4: A. Pinch test showing that it does not compromise closing the palpebral rim. **B.** Marking with a minimum of 4mm above the ciliary border in order not to block lymphatic drainage.

Chart 2: Preparation of anesthetic and cooling solutions

Anesthetic solution	Cooling solution
Add the following to a 10ml syringe:	Add to a 20ml syringe:
3ml lidocaine, 2%	2.5ml dexamethasone
5.6ml saline solution, 0.9%, 0.4ml sodium bicarbonate, 8.4%	15ml sodium chloride, 0.9% (saline solution)
0.2ml adrenalin	
Available in this solution: 60mg of lidocaine and 200µg of epinephrine	

***Note.: The commercial formulation of 2% lidocaine with epinephrine 1:200000 provides 15µg of epinephrine, so the above-mentioned solution has a 13-fold vasoconstrictive power.

Chart 3: Surgical instruments

Scalpel handle
No. 15 Blade
Gilles skin hook
Toothed forceps
Delicate curved scissors
Delicate curved Kelly
Widia needle-holder
Electrocautery

Use a 3ml syringe with a 30G needle. Pass the solution from the 10ml syringe (the 10ml syringe will always be used for the anesthetic solution and the 20ml syringe for the cooling solution). Use one needle for each side to always maintain an ideal thread in the first puncture. Prior organization of the surgical procedures clearly decreases the propensity to errors.

Conduct the punctures first along the supratarsal line to make a path for punctures, confirming the prior ink marking, return to the ipsilateral lateral canthus and trace the superior line of the plane. Hydro-dissect the center of the surgical plane.

Mean volume used is 3ml per side.

After anesthesia, wait 15 minutes in order to obtain the proper vasoconstrictive effect.

Anesthetize the contralateral side in the same way. Incision: medial to lateral, bringing the incision towards yourself.

The canthi should end at sharp angles, less than 45 degrees.

Using toothed forceps, begin dissection of the skin. The removal should be delicate, because the skin is extremely thin (Figure 5a).

The excised skin should be kept in a kidney tray with saline solution (in case of need, serving as skin for grafting).

After removal of the skin, the orbicularis oculi muscle appears, especially its preseptal portion (Figure 5b).

Delicate pressure is exerted on the eyeball to assess the filling caused by the antero-superior shifting of the fat pads which are still contained by the fibrous septum and the orbicularis oculi muscle.

The curved scissor is used to remove linear portions of orbicularis oculi muscle in which there was turgidity caused by the pads.

This begins in the projection of the central or medial pad, which is a pre-aponeurotic fat pad and is easily identified. It is goldish-yellow in color (Figure 6a).

The pad can be seen due to the transparency of the septum covering it. The septum is thin, and the pad has a soft appearance

Dissect the medial pad delicately with the help of a straight Kelly forceps with gauze wrapped around the tip, holding the pad with the toothed forceps. It is helpful to anesthetize the pad's pedicle before grasping it. With the help of the toothed forceps, pull the pad and anesthetize its "pedicle" (actually the most proximal portion of the pad).

Soft pressure on the eyeball facilitates the pad's exposure. Care and attention are necessary with bradycardia due to parasympathetic stimulus (Figure 6b).

After dissection of the pad, pressing the eyeball, the pad is clamped by its pedicle with the curved Kelly forceps, pretested for its grasping capacity as shown in Figure 6c.

Cut the pad with the curved scissors on the concave side of the Kelly forceps. The Kelly forceps is thus closed with the fat pad's pedicle between its serrated jaws and the rest below it (Figure 6d).

Generous electrocoagulation is performed then with the electrocautery along the entire length of the jaws of the Kelly forceps, which are holding the remainder of the fat pad. Immediately after electrocoagulation, cooling is performed with the cooling solution.

This is the key moment in the surgery, in which the surgical assistant keeps constant gentle pressure on the eyeball and the Kelly forceps is opened. The surgeon verifies whether there is any bleeding in the fat pad, specifically prior to its grasp by the Kelly forceps. Electrocoagulation is performed on this portion, which is cooled again, and the assistant gently releases the pressure on the eyeball in order to allow retro-inferior retraction of the fat pad.

The same is done with the nasal pad. However, the nasal pad is deeper than the medial pad. The dissection should be performed very cautiously and gently. Again, pressure on the eyeball is required. Exteriorization of the nasal pad is more difficult, but more orderly, due to its greater consistency. The nasal pad is paler, denser, and more compact than the medial fat pad and is more protected by the fibrous septum.

Anatomical knowledge of the position of the tendon of the superior oblique muscle is important, located below the pad in order to avoid unintended trauma to this structure, which can cause strabismus and diplopia.[15]

During dissection of the nasal pad, the patient may feel

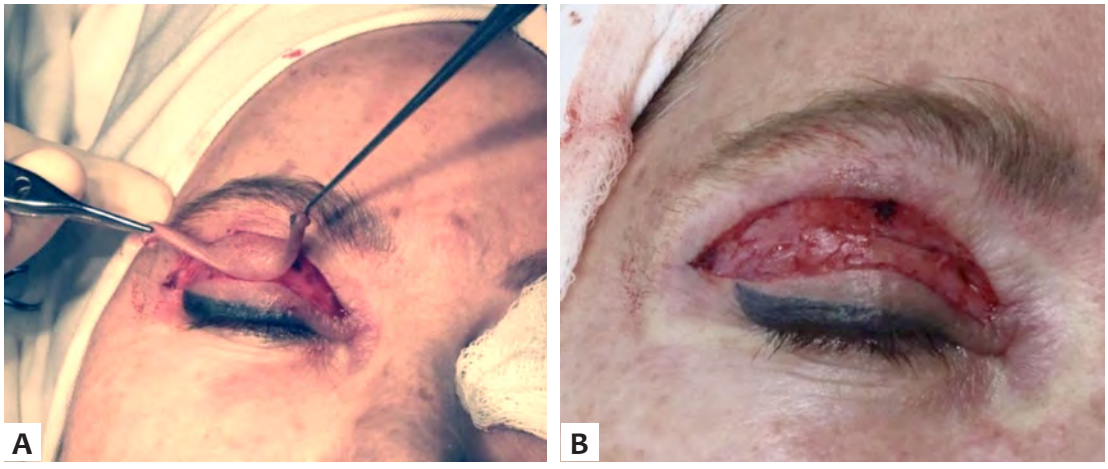

Figure 5: A. Dissection of skin with help of Gilles hook. **B.** Orbicularis oculi muscle after total removal of skin

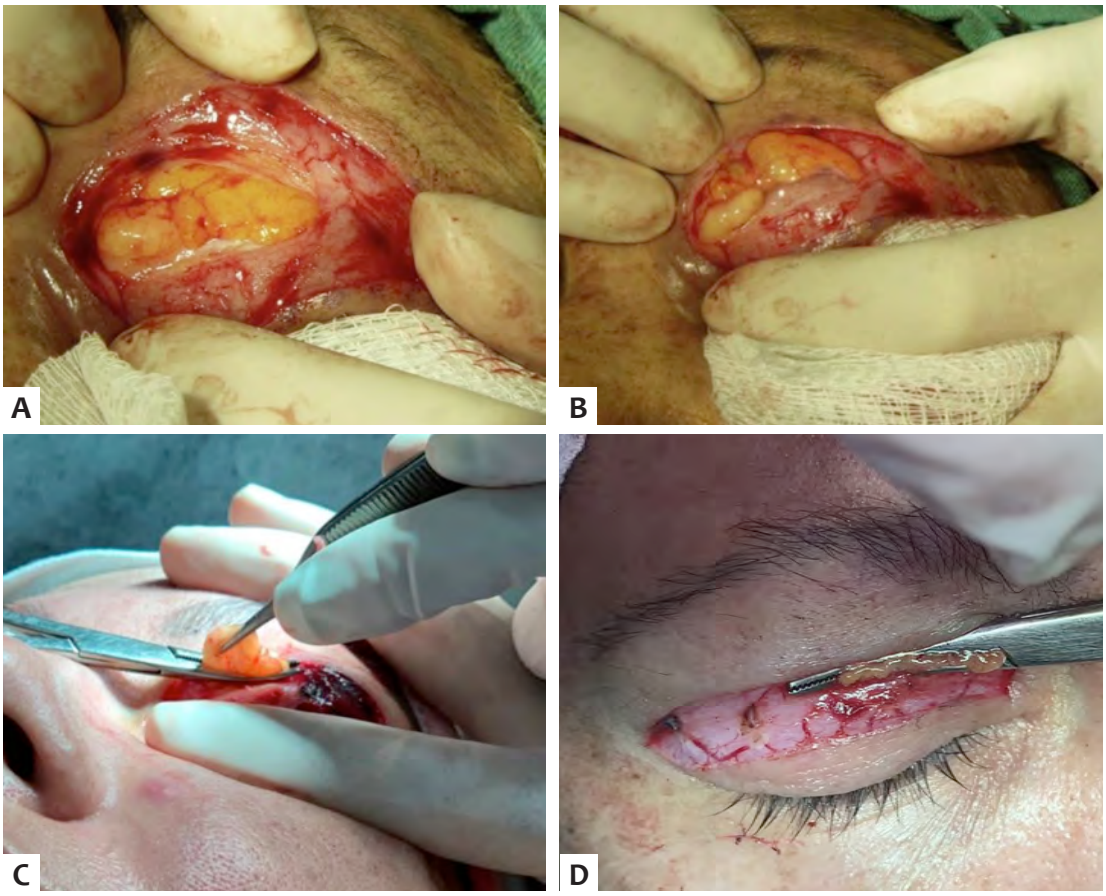

Figure 6: A. Medial or central pad. **B.** Gentle pressure on eyeball, facilitating exposure of the fat pad. **C.** Fat pad clamped with Kelly forceps. **D.** Kelly forceps closed with fat pad pedicle between the jaws.

some pain and discomfort, even with prior infiltration with the anesthetic solution.

Great care and attention are necessary in clamping the nasal pad's "pedicle" with the curved Kelly forceps, in relation to the above-mentioned tendon. Only the pad should be clamped.

Infiltration of anesthesia in the pad leaves it more tumescent and visible, and projects it more efficiently.

Again, the scissors rests against the concave side of the Kelly forceps and cuts the portion above the forceps.

Pressure is maintained to perform rigorous electrocoagulation and cooling, with immediate hemostasis. With pressure still on the eyeball, the jaws of the Kelly forceps are opened, with extreme attention to the presence of bleeding. Again, electrocoagulation is performed on the remaining portion of the fat pad, Cooling is performed, and the eyeball is decompressed to return the nasal pad's pedicle to its superior and retrobulbar position.

Any bleeding from the pads' "pedicles", if left undetected and untreated, can lead to retrobulbar hematoma, an emergency situation with the risk of blindness and which requires immediate resolution, preferably by the ophthalmologist.

Some surgeons rigorously remove large extensions of the pads. Good results require removal of an excessive portion of the fat pads. Prior clinical assessment, and assessment at the moment of the decision on clamping, are essential for deciding how much of the pads should be removed.

A careful inspection is now made of the entire region. Direct visualization of the pads is not possible, since they have returned to their original position.

Electrocoagulation is performed on any bleeding points, which can be done from medial to central along the orbicularis oculi muscle to produce its retraction, on the line where the final scar will be located.

With the help of the Gilles hook and fine-tipped scissors, release the skin from the borders of the surgical plane to facilitate and optimize healing.

Edge-to-edge suture is performed with nylon 6.0 and simple or running intradermal sutures. The results are similar.

Having concluded the suturing, a cold compress is placed on the area. A practical approach is to tie two surgical gloves together by their wrists, filled with water, and freezing them in advance. The gloves are positioned over the eyelids with the fingers pointing outwards, as shown in Figure 7, providing both cooling and gentle compression from the gloves' weight. The eyelids should be protected with cotton gauze.

The longer tips of the sutures should be properly positioned in relation to the eyebrow to keep the thin, stiff tips from

bothering the patient.

Raise the head of the gurney and then the patient's bed and keep the compress cold.

Offer a light diet after 40 minutes, check vital and physiological signs, and if the patient is oriented in time and space, discharge is allowed.

The patient should continue to rest and follow the instructions provided during the preoperative visit.

Stitches may be removed on approximately day 5.

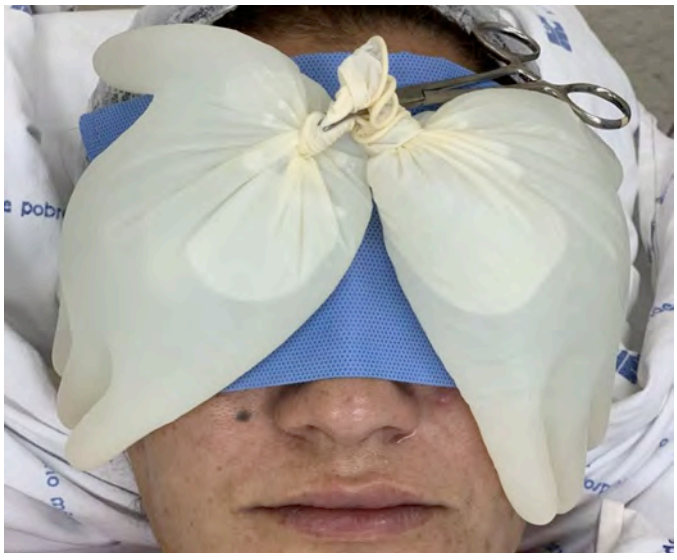

Figure 7: Use of surgical gloves for cooling and gentle compression

RESULTS

In the cases described here, the stitches were removed after five days, with no postop complications.

There was expected edema and ecchymosis, but no pain Two months after the surgery, good results were observed, with maintenance of correct positioning of the eyelids and absence of irritative symptoms in the eyeball (Figures 8, 9, and 10).

DISCUSSION

Blepharoplasty provides relief of the tired-looking face, signs of aging, and midface ptosis.

With aging, the eyelids' skin tends to sag and the eyes' supporting musculature loses its tone, tending to form fat pads under the eyelids. The sagging musculature, excess skin, and herniation of the fat pads produce a tired, aged appearance.

Blepharoplasty is a surgical technique that produces great benefits and patient satisfaction by attenuating the flaccidness and palpebral ptosis, when used alone or in combination with other currently available treatments.

Since blepharoplasty can be performed under local anesthesia, without sedation, it may be considered a simple surgery, without complications and with low morbidity, as long as properly indicated and performed correctly with all the necessary

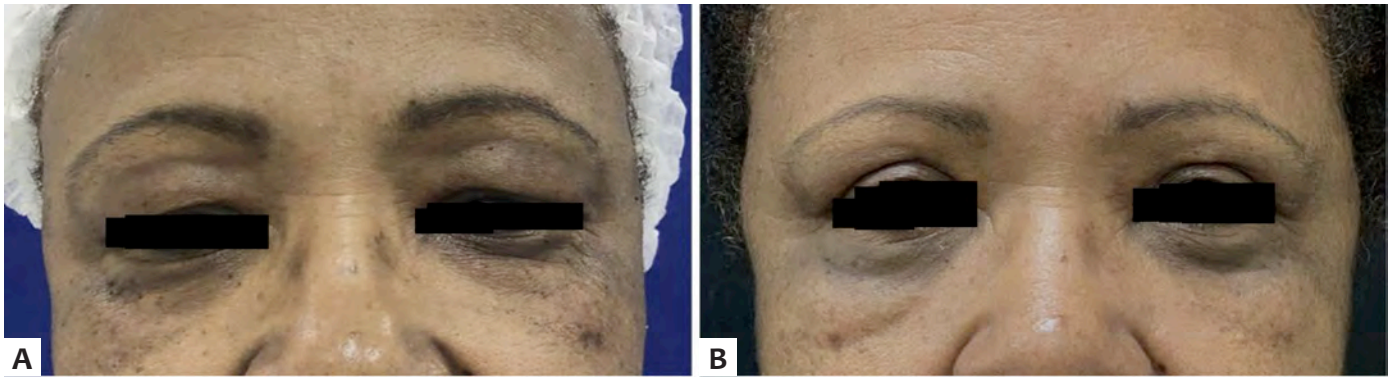

Figure 8: A. Patient in preoperative view for upper blepharoplasty. **B.** Patient in postoperative view, upper blepharoplasty

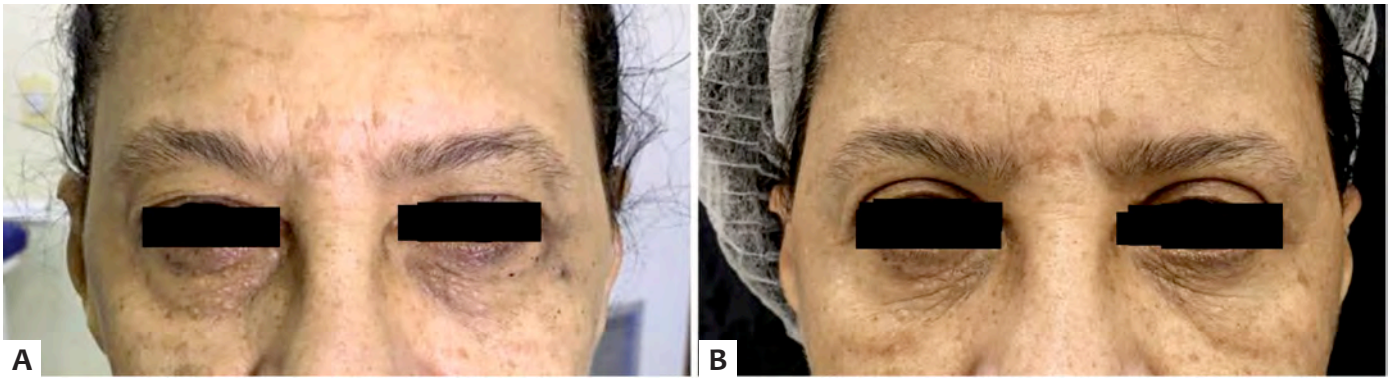

Figure 9: A. Patient in preoperative view for upper blepharoplasty. **B.** Patient in postoperative view, upper blepharoplasty

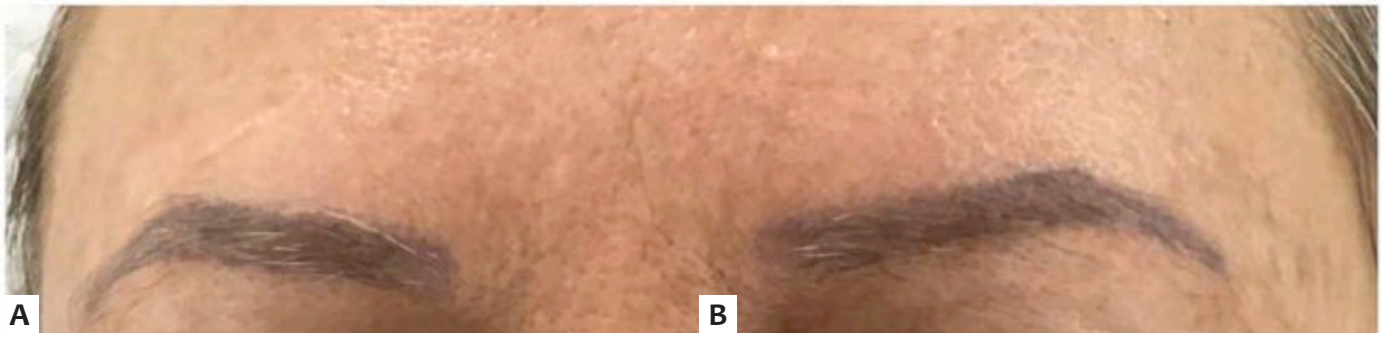

Figure 10: A. Patient in preoperative view, upper blepharoplasty. **B.** Patient in postoperative view, upper blepharoplasty

care.

Blepharoplasty not only gives the patient a younger appearance, but also meets a functional need by lending a less tired expression and improving the field of vision.

CONCLUSION

The dermatological surgeon who is accustomed to removing carcinomas from the eyelids and performing concomitant reconstruction has already done reconstructive blepharoplasties, although perhaps without realizing it. Reconstructive surgery of eyelids after removal of a cancer is certainly more complex than when performed for aesthetic reasons and with prior markings and planning.

Proper preoperative assessment, detailing the surgery's benefits and limitations, avoids problems and false expectations. This has shown that blepharoplasty is a safe and effective option with good functional and aesthetic results, low complication rates, and good acceptance by patients. ●

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Clinical comparison between topical benzoyl peroxide 2.5% and diclofenac gel 1% versus benzoyl peroxide 2.5% and placebo in the treatment of mild to moderate facial acne vulgaris

Comparação clínica entre peróxido de benzoília tópico 2,5% e diclofenaco gel 1% versus peróxido de benzoília 2,5% e placebo no tratamento da acne vulgar facial leve à moderada

DOI: http://dx.doi.org/10.5935/scd1984-8773.20201211439

ABSTRACT

Introduction: The inflammation may play a critical role in the development of facial acne. Pro-inflammatory mediators, such as prostaglandins and leukotriene, have been implicated in the initiation of acne.

Objective: This study aimed to evaluate the clinical efficacy and safety of 1% diclofenac gel compare with a placebo gel in the treatment of mild to moderate acne patients in 12 weeks.

Methods: A 12 weeks, randomizing, double-blind, individual and split-face comparative trial was conducted in 24 volunteers. Patients with mild to moderate acne vulgaris, aged 18 to 30 years were enrolled. They received 2.5% benzoyl peroxide with 1% diclofenac gel and 2.5% benzoyl peroxide with placebo gel apply regularly at each side of the face.

Results: 24 participants with mean (SD) age of 25.92 years were enrolled in the study. Statistically significant decrease in mean of comedone lesions was observed in 1% diclofenac gel group by acne lesion count at week 12 (P <0.05) superior than placebo gel. Moreover, post inflammatory hyperpigmentation also had statistically significant decrease superior to placebo group at week 4.

Conclusions: The 1% diclofenac gel topical treatment has shown good clinical efficacy and safety in decreasing facial comedones at week 12 and post-inflammatory hyperpigmentation in 4 weeks.

Keywords: *Acne vulgaris; Diclofenac; Inflammation; Hyperpigmentation*

RESUMO

Introdução*: A inflamação pode desempenhar um papel crítico no desenvolvimento da acne facial. Mediadores pró-inflamatórios, tais como prostaglandinas e leucotrieno, têm sido implicados no início da acne.*

Objetivo: *Este estudo teve como objetivo avaliar a eficácia clínica e a segurança do diclofenaco gel 1% comparado ao gel com placebo no tratamento de pacientes com acne leve à moderada, durante 12 semanas.*

Métodos: *Um estudo comparativo de 12 semanas, randomizado, duplo-cego, individual e split-face foi realizado em 24 voluntários. Foram incluídos pacientes com acne vulgar leve a moderada, com idade entre 18 e 30 anos. Os pacientes receberam peróxido de benzoíla 2,5% combinado com diclofenaco gel 1% ou peróxido de benzoíla 2,5% com gel de placebo, aplicados regularmente em cada lado da face.*

Resultados: *24 participantes com idade média (DP) de 25,92 anos foram incluídos no estudo. Foi observada uma diminuição estatisticamente significativa na média de comedões no grupo em uso de diclofenaco gel 1%, através da contagem de lesões de acne na semana 12 (P<0,05), superior ao gel de placebo. Além disso, a hiperpigmentação pós-inflamatória também apresentou diminuição estatisticamente significativa superior ao grupo placebo na semana 4.*

Conclusões: *O tratamento tópico com diclofenaco gel 1% mostrou boa eficácia clínica e segurança na diminuição dos comedões faciais na semana 12 e na pós-hiperpigmentação inflamatória após 4 semanas.*

Palavras-chave: *Acne vulgar; Diclofenaco; Inflamação; Hiperpigmentação*

Original Articles

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INTRODUCTION

Acne vulgaris is a common chronic skin disorder of the pilosebaceous unit that is usually involved with adolescents.[1] Acne vulgaris has several main factors including inflammation which is emerging recently because of the antibiotic overuse and resistant of bacteria.[2] The course of acne may be self-limited, but it is a distress condition among young adult who is sensitive about their appearance and also may lead to permanent scarring.[3,4]

Inflammatory signaling in the pilosebaceous unit is a component of the initiation of acne lesions. The microcomedone, which arises from keratinocyte occlusion, is believed that inflammation may precede microcomedone formations and trigger follicular plugs. The study of acne-prone patients and early acne lesions shows increasing in perifollicular and papillary dermal CD3+, CD4+ T cells, the proinflammatory cytokine IL- 1, and many proinflammatory signals in the uninvolved skin.5 P.acnes induces inflammation by stimulating via TLRs, and it activates the up-regulation of TLR2 and TLR4. TLR2 of macrophages are induced to release multiple proinflammatory cytokines and chemokines: interleukin- 8 (IL- 8) , tumor necrosis factor- alpha (TNFα) , interleukin- 1 alpha (IL- 1α) , interleukin- 12 (IL-12), interleukin-1 beta (IL-1β).6,7 Then, the pathogen will be attacked by PMNs or NKs cell and/ or antimicrobial peptides (AMPs).[8]

Moreover, inflammation is induced via the cyclooxygenase metabolic pathway and the lipoxygenase pathway.9 The key mediator of inflammation in COX pathway is prostaglandins; it significantly aggravates inflammation and also stimulate sebaceous proliferation and sebum production via PPAR- mediated pathways.[10,11] LTB4, LOX pathway, activates the local attraction of neutrophils and monocytes.[11] Moreover, LTB4 stimulates DNA synthesis and keratinocyte proliferation which is the early acne lesion.[12] Diclofenac, NSAID, is proven to have analgesic, anti-inflammatory, and antipyretic properties and show dual action on COX and LOX inhibitors.[13,14] Inhibiting LOX and COX pathway may be another way to treat acne disorder.

Acne lesions prone to resolve with sequelae. Production and release of various keratinocyte-derived mediators, including prostaglandins, leukotrienes and many cytokines that affect melanocyte proliferation and melanin production are promoted by inflammation of the epidermis.[15] Although PIH usually spontaneous resolves, but it can last from months to years.[16] Since the hyperpigmentation is a consequence of the inflammation, it is important to control the inflammation effectively for preventing and reduce the severity of PIH.[16]

In this study, the authors aimed to evaluate the clinical efficacy and safety of facial acne vulgaris reduction, post inflammatory hyperpigmentation and quality of life with acne in male and female aged 18-30 years old using anti-inflammation effect of 1% diclofenac gel. The reduction of acne lesion counts and acne severity is the primary endpoint.

METHODS

A. Study design

This study was designed as a single center, randomizing, double-blind, individual and split-face comparative trial. This study was conducted at the outpatient dermatology clinic of Benchakitti Park Hospital between October 2018 to April 2019. This study was approved by the Human Ethics Committee of Thammasat University.

B. Study participants

Seventeen women and seven men with a mean age of 25.92 years were enrolled (N=25). Eligible subjects had Fitzpatrick skin types II-V with mild to moderate facial acne vulgaris. The acne vulgaris is evaluated by acne lesion counts and global acne severity index. Subjects were asked to avoid any other moisturizer or cosmetic product that have acne reduction effect during the study.[13] The exclusion criteria are subjects with severe acne disease, severe systemic disease, known allergy to NSAIDs, history of hirsutism, polycystic ovarian disease or significant menstrual irregularities, pregnancy and lactating. Subjects are using systemic antibiotics, topical corticosteroids, oral contraceptive pill, and systemic retinoid will be excluded. One patient not complete the trial due to personal issue that cannot come to follow up (N=1).

C. Methods

In this study, the treatment will be assigned to each patient randomly according to the intervention group. The intervention group will get 1% diclofenac gel to apply on one side of the face twice a day with 2.5% benzoyl peroxide applied to both sides of the face daily before bed. Along with prescribing broad spectrum anti-UVA and anti-UVB sunscreens to apply adequately every day. Other topical applications or cosmetic products that will affect the result will be prohibited throughout the study.

D. Assessments

The primary clinical efficacy endpoint is the change from baseline in facial acne vulgaris at week 12 by acne lesion count and global acne severity score. The secondary endpoint are drug local-tolerability and reduction of post inflammatory hyperpigmentation by Antera 3D® image (Miravex Ltd, Dublin 2, Ireland). Focus area of Antera 3D® image (Miravex Ltd, Dublin 2, Ireland) will be taken on the same point by using the intersection line between the imaginary line from lateral cantus to alar of nose. The photograph will be taken at the baseline and every visits by using digital camera (CANON60D) in the identical camera setting, lighting and fixed patient positioning. Moreover, the subjects were asked to answer dermatology life quality index and Cardiff acne disability index to evaluate mental impact of acne disorder.

Statistical analyses

The demographic data were analyzed using standard descriptive statistics. The change from baseline in facial acne vulgaris, post inflammatory hyperpigmentation and life quality index were presented as mean (95% confidence interval). P-value corresponds to Paired t test with < 0.05 was considered statistically significant.

RESULTS

Among twenty-four participants with mild to moderate facial acne vulgaris were enrolled into the study. Baseline demographic data was shown in (Table 1).

At baseline, the mean number of acne counts were not significantly different between treatment groups. Both groups have acne severity and acne count not significantly different. Among patients treated with 2.5% benzoyl peroxide/1% diclofenac gel, the mean (SD) baseline comedone lesion count was 15.13, decreasing to 4.25 after 12 weeks while the mean baseline comedone lesion count of 14.5 for placebo-treated patients decreased to 6.13. The number of comedone acne is reduced significantly in both group in week 2, week 4, week 8, and week 12. There is no different of comedone treatment efficacy between the intervention group and placebo group except in week 12 that the intervention group shows significantly superior than placebo group (P<0.001). (Figure 1)

Secondly, the mean (SD) baseline papule and pustule lesion count was 3.33, decreasing to 1.71 after 12 weeks while the mean baseline papule and pustule lesion count of 3.13 for placebo-treated patients decreased to 1.96. The reduction of papule and pustule acne is constantly improving in both groups. The intervention group has significantly reduced number of papule and pustule at week 12, but it does not show superior significant between the intervention group and placebo group.

Third, the mean (SD) baseline cystic and nodular acne lesion count was 0.5, decreasing to 0.38 after 12 weeks while the mean baseline cystic and nodular acne lesion count of 0.75 for placebo-treated patients decreased to 0.63. The reduction of cystic and nodular acne is constantly improving in both groups. The placebo group has significantly reduced number of cystic and nodular acne at week 2, week 4 and week 8, but it does not show superior significant between the intervention group and placebo group.

TABLE 1: BASELINE DEMOGRAPHIC DATA

	Total (N=24)
Age (years)	
Mean (SD	25.92
Range	18-30
Sex, N(%)	
Men	7 (29.2%)
Female	17 (70.8%)
Global acne severity score, N(%)	**N(%)**
Mild	19 (79.2%)
Moderate	5 (20.8%)

Melanin reduction by Antera 3D® image

The Antera 3D assessments for melanin shows improvement of melanin color after 12 weeks in both intervention and placebo group. Among 2.5% benzoyl peroxide/1% diclofenac gel-treated patients, the mean (SD) baseline PIH lesion was 0.4, reduce to 0.36 after 12 weeks while the mean baseline PIH lesion of 2.5% benzoyl peroxide/ placebo gel group was 0.42 reduce to 0.38. There is no different at the baseline of both groups. At week 4, the 2.5% benzoyl peroxide/1% diclofenac gel group show the superior reduction of hyperpigmentation score superior over 2.5% benzoyl peroxide/ placebo gel group significantly. At the end of the study, the hyperpigmentation score does not show statistically significant difference between both groups. (Figure 2)

Side effect evaluation

The side effect was scored by patient and physician using side effect questionnaire. Both physicianand patient evaluation about severity of scaling, erythema, burning, stinging, and itching scoring are quite similar. The side effect remained low for both groups, and severity scores range in 0 or 1 for 80 to 90 percent of patients at the end of study. The most common side effect is mild erythema and scaling. This mild side effect did not lead to discontinuation of treatment. The improvement score

The improvement score was recorded by patients and physician. For the patient's perspective on intervention side, the mean (SD) baseline of acne improvement is 1-25% improvement. After 12-week treatment, the mean (SD) of acne improvement is 26-50% improvement. For placebo side, the mean (SD) baseline of acne improvement is 1-25% improvement and 1-25% improvement at week 12. Both the intervention group and placebo group have significant improvement of acne at week 12, but it does not show superior significant between the intervention group and placebo group.

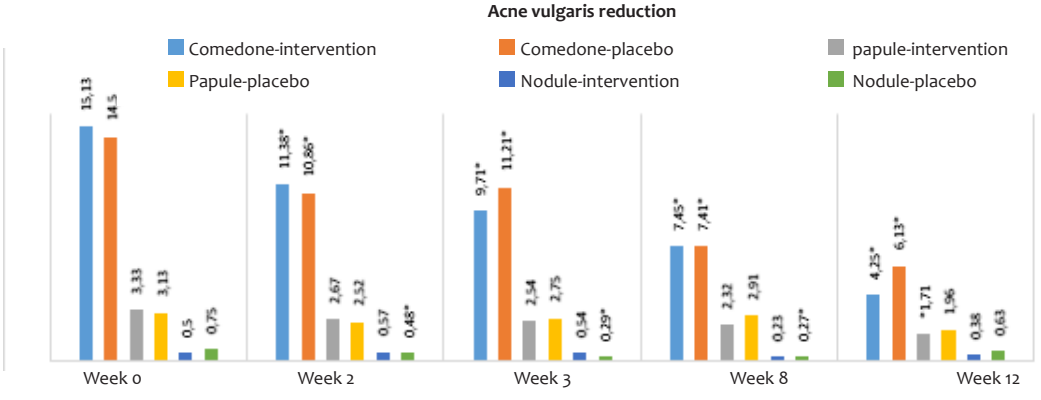

FIGURE 1:
Mean change from baseline to week 12 of acne lesion count

*p < .05 is derived from the paired t-test

For doctor perspective on intervention side, the mean (SD) baseline of acne improvement is no improvement. After 12-week treatment, the mean (SD) of acne improvement is 1-25% improvement. For placebo side, the mean (SD) baseline of acne improvement is no improvement. After 12 weeks' treatment the mean (SD) of acne improvement is 1-25% improvement. Both the intervention group and placebo group have significantly improvement of acne at week 8 and week 12, but it does not show superior significant between intervention group and placebo group. In addition, the overall treatment satisfaction is 7.63 out of 10 at 12 weeks.

The Cardiff Acne Disability Index (CADI) and the Dermatology Life Quality Index (DLQI)

For acne induced quality of life impairment by CADI score, CADI 1-5 is mild impairment, CADI 6-10 is moderate impairment, CADI 11-15 is a severe impairment. At week 0, there was mild impairment (CADI=1-5) for feeling aggressive, frustrated, or embarrassed on acne. There was significantly reduce in impairment of embarrassment, interfere with social life and relationship, the concern of appearance and acne disturbing. There was mild impairment of wearing swimming costumes. There was mild impairment of concerning the appearance. Patients acne severity considers mild impairment (CADI=1-5). (Table 2)

The Dermatology Life Quality Index

To evaluate impact of acne on daily life is measure by DLQI, 0-1 = No effect on patient's life, 2-5 = mild effect, 6-10 = moderate effect, 11-20 = very large effect, 21-30 = extremely large effect. The result shows only mild effect of acne to the patient's quality of life.

DISCUSSION

Acne vulgaris is one of the most common skin disorder which commonly located on the face, chest, and back. It is predominantly among adolescents, at 15-18 years old.17 The goal of treatment is finding the cause of acne, reduce acne severity, prevent new acne formation, lessen psychological distress and scarring.18 Some of the acne patients find it is a stressful disorder that can lead to depression and lack of self-esteem.3 The DLQI study of 110 acne patients in Thailand, the mean total DLQI score was 8.95 (range 0-24). The most disturbing from acne is an embarrassment. This study only shows mild impairment. Similarly, the most disturbing is an embarrassment or self-consciousness. In addition, this study also evaluated CADI. The patients reported mild impairment from acne. After the treatment, the patients report lessen anxiety, lessen effect on their daily life, lessen interfering social life and lessen concern of appearance significantly.

Inflammation has been recognized as one of the major factor initiated acne. The study of acne-prone patients and early acne lesions shows increasing in perifollicular and papillary dermal CD3+, CD4+ T cells, the pro-inflammatory cytokine IL-1, and many proinflammatory signals in the uninvolved skin.[5] The innate immune, when pathogen, P.acnes, slip through epidermis will be quickly recognized by TLRs and then attacked by cells (PMNs or NKs) and/or secreted substances like antimicrobial peptides (AMPs).[9] TLR-2 and TLR-4 are responsible for acne pathogenesis.[6] Up-regulated AMP induces pro-inflammatory chemokines and cytokines and also stimulates keratinocyte production.[5] P.ac-

TABELA 2: MEAN CHANGE FROM BASELINE IN THE CADI BEFORE AND AFTER THE STUDY

	Antes do estudo	Depois do estudo	Valor de p
Flet aggressive, frustrated, or embarrassed on your acne	242±1,18	1,88±0,95	0,038*
Acne has interfered with your social life and relationship with the opposite sex	2,46±0,98	2,08±0,88	0,033*
Avoided wearing swimming costumes or clothes which may expose areas of your trunk with acne	1,63±0,92	1,33±0,56	0,052*
Been concerned about the appearance of your acne	2,71±1	2±0,83	<0,001*
Acne disturbant	2,42±0,97	2±0,78	0,013*

* p < .05 is derived from the paired t-test.

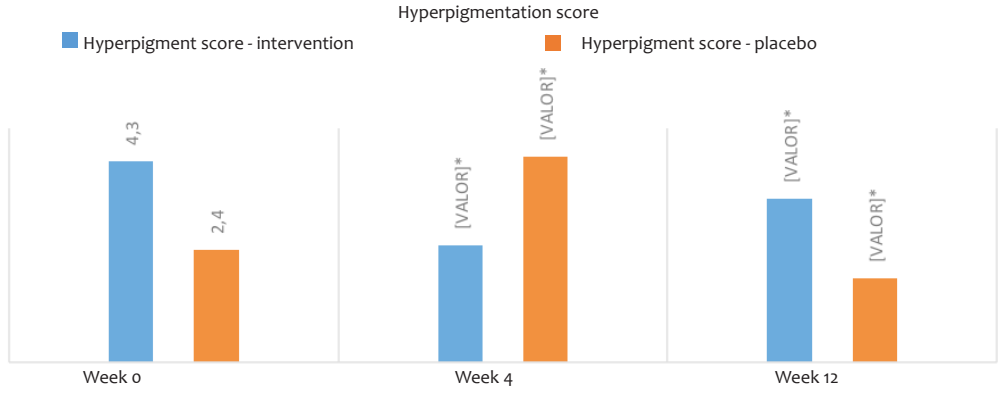

FIGURE 2:
Mean change from baseline to week 12 of acne lesion count

*p < .05 is derived from the paired t-test.

nes enhances sebaceous lipogenesis, which oxidized and induce production of inflammatory mediators in cultured keratinocytes.[5] Other proinflammatory lipid by-products, AA, is metabolized into prostaglandins (PG), and leukotrienes (LT).[8] LTB4 attract local neutrophils and monocytes.[11] PGE2 stimulates the formation of histamine and bradykinin.[19] This suggested that COX and LOX pathway induced inflammation in acne which opened new opportunities for acne treatment. (Figure 3)

The diclofenac, NSAIDs, is an anti-inflammatory drug that appears to have both effect on lipoxygenase pathway and cyclooxygenase pathway.[20] The former study demonstrated that mice without LTB4 receptor have lower inflammation.[20] The study of banoxaprofen show improvement of acne disorder.[21] A study of tetracycline hydrochloride capsules with ibuprofen tablets (2,400 mg/day) for 2 months demonstrated an effective result. Another study combine minocycline capsules (150 mg/day) and ibuprofen tablets (1,200 mg/day) also demonstrate very good result.[22] Rofecoxib 50 mg daily prophylaxis premenstrual acne. 101 patients show significant decrease in inflammatory acne by zileuton.[23] Explained this study that 1%diclofenac gel, COX and LOX pathway inhibitor, might help subside a small inflammation which there is an improvement of comedone statistically superior than placebo group. However, papule/pustule and cystic/nodule acne show promising result yet not statistically superior than placebo group. In addition, the results also show decreasing number of acne in both intervention and placebo group. This may due to 2.5% BPO, which is standard treatment of acne. A greater different in acne count may show if the study has larger group of patients.

The most common side effect in this study is mild scaling and erythema. Both intervention and placebogroup have no statistically different. These side effects are caused by both BPO and 1%diclofenac gel. The incidence of adverse events was 84.0% in the 2.5% BPO group of 450 Japanese volunteer in 52 weeks.[24] Diclofenac treatment was well tolerated, patients reported 'fair' to 'excellent' tolerability. Some of patients experienced usually mild local reactions, for example, skin dryness, erythema, and pruritus.[25] The higher the concentration of diclofenac leads to more side effect.[26] In conclusion, 1% diclofenac gel to the limitations are that this is merely a small study with small sample size. The long-term follow up and larger number of patients are suggested to confirm the efficacy and safety.

Treat mild to moderate acne is safe with low adverse event.

The former study shows inflammatory factor has influence over melanocyte proliferation.[27] Moreover, PGE2, and PGD2, is responsible for activation and /or proliferation of epidermal pigment cells.[28] COX-2 knock-down in melanocytes resulted in decreased expression of tyrosinase, tyrosinase-related protein 1(TRP-1) and melanogenesis Associated Transcription Factor (MITF), as well as reduced tyrosinase enzyme activity.[29] This study shows significant improvement of hyperpigmentation score of intervention group superior to placebo group significantly at week 4. However, at the end of the study, the hyperpigmentation score does not show statistically significant difference between both groups. This might suggest that 1%diclofenac gel help reduce melanin faster than placebo gel.

Furthermore, despite inflammation factor, there are several factor that have impact to acne disorder.[2] To achieve the goal of facial acne vulgaris treatment need several modality of treatment. 1%diclofenac gel is suggested to be one of the alternative treatment of mild to moderate facial acne vulgaris. Better understanding of inflammation process would help create new possibility of acne treatment in the future

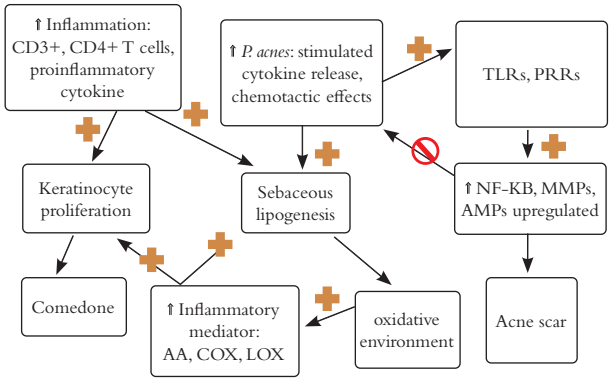

Figure 3: Inflammation and Acne vulgaris

CONCLUSION

This randomized, split face, double-blind study demonstrated that 2.5% benzoyl peroxide/1% diclofenac gel is an effective and safe treatment option for patients with comedone. There was a statistically significant decrease in comedone lesions, and the medication causes little to no irritation. This study also suggests 2.5% benzoyl peroxide/1% diclofenac gel helps reduce post inflammatory hyperpigmentation after 4 weeks. Although the study of papule/pustule and nodule/cystic acne were not statistically significant. However, the result show little improvement to all lesions. The data consistently favoured 2.5% benzoyl peroxide/1% diclofenac gel over placebo to treat acne vulgaris and post inflammatory hyperpigmentation.

This study is the first to my knowledge to demonstrate the clinical efficacy and safety of primary and secondary outcomes of the change from baseline of acne vulgaris and PIH in 18-30 years' women and men that have mild to moderate facial acne vulgaris by the assessment of acne lesion count, GAGs and Antera 3D® image. This study can be a valuable study that help research about inflammation and acne vulgaris in the future. However, ●

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Treatment of median sternotomy scars using Triamcinolone injections, Silicone Dressings and a combination group: a prospective randomized comparative study

O tratamento das cicatrizes de esternotomia mediana com injeções de triancinolona, placas de silicone e terapia combinada: um estudo prospectivo randomizado

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ABSTRACT

Introduction: Silicone dressings and Triamcinolone injections are known to improve keloids and hypertrophic scars size, erythema, flexibility, and symptoms such as pain and itching. These treatments are non-invasive, inexpensive, and widely used as first or second-line therapy; however, studies comparing them are still lacking.

Objective: To compare silicone dressings, triamcinolone injections, and a combination group, to treat hypertrophic scars, at the same anatomical area, caused by the same mechanism of injury.

Materials and methods: In a prospective study, 12 patients with median-sternotomy scars were randomized into 3 groups (n=4 patients each): group 1, monthly triamcinolone injections; group 2, a combination of silicone dressings and triamcinolone injections; and group 3, silicone dressings. Patients were evaluated in monthly clinical appointments using the Vancouver Scale and the durometer. Immunohistochemistry and confocal microscopy for collagen types I and VI were performed in scar samples. The groups were compared using Kruskal-Wallis and Friedman tests, with $p<0,05$ indicating significance.

Results: The three treatments were effective in reducing the Vancouver scores. A difference between the three groups was observed at time 2 when triamcinolone was less effective. Group 2 showed an improvement on pigmentation ($p = 0,042$). Collagens types I and VI presented increased fluorescence throughout the superficial and deep dermis in untreated lesions, which decreased after the treatment. Although the number of patients is limited, this is the first prospective study addressing some of the major bias in scars treatment.

Keywords: Scar; Keloid; Silicone gel; Triamcinolone

RESUMO

Introdução*: Placas de silicone e injeções de triancinolona melhoram o tamanho dos queloides e das cicatrizes hipertróficas, além do eritema, da elasticidade e de sintomas como dor e prurido. Esses tratamentos nao sao invasivos, têm um bom custo-beneficio e são amplamente utilizados como terapia inicial para queloides e cicatrizes hipertróficas; entretanto, faltam estudos comparativos dos dois tratamentos.*

Objetivo*: Comparar o uso de placas de silicone, triancinolona intralesional, e a combinação de ambas as modalidades terapêuticas, no tratamento de cicatrizes hipertróficas na mesma área anatômica e causadas pelo mesmo mecanismo de lesão.*

Métodos e Materiais: *Em um estudo prospectivo, 12 pacientes com cicatrizes de esternotomia mediana foram randomizados em 3 grupos (4 pacientes em cada grupo): Grupo 1. injeções mensais de triancinolona; Grupo 2. uma combinação de placas de silicone e injeções de triancinolona e Grupo 3. placas de silicone. Os pacientes foram avaliados em consultas clínicas mensais com o uso da Escala de Vancouver e durômetro. Foram realizadas imunohistoquímica e microscopia confocal para os colágenos de tipos I e VI em amostras de cicatriz. Os grupos foram comparados com os testes de Kruskall-Wallis e Friedman com significância de $p< 0.05$.*

Resultados: *Os três tratamentos mostraram-se eficazes na melhora das cicatrizes, conforme demonstrado pela redução nos parâmetros da Escala de Vancouver. Foi observada uma diferença entre os três grupos no tempo 2, quando a triancinolona mostrou-se menos eficaz. O grupo 2 apresentou melhora na pigmentação ($p = 0,042$). Os colágenos de tipos I e VI apresentaram aumento de fluorescência em toda a derme superficial e profunda nas lesões não-tratadas, que diminuiu após do tratamento. Apesar do número pequeno de pacientes, este foi o primeiro estudo prospectivo que comparou estas modalidades de tratamento de cicatrizes, evitando vieses frequentemente vistos em publicações sobre tratamentos de cicatrizes.*

Palavras-chave: *Cicatriz; Queloide; Gel de silicone; Triancinolona*

INTRODUCTION

Since the first reports on the use of silicone gel dressings in hypertrophic scars and keloids in 1983[1], several authors have shown that this noninvasive treatment modality improves scar size, pliability, erythema, pain, and itching[2] by increasing skin hydration and occlusion[3]. Since silicone dressings are relatively inexpensive, noninvasive, and have very mild side effects, they have become one of the first-line treatments for keloids and hypertrophic scars.

Intralesional corticosteroid injections are also used to treat keloids and hypertrophic scars, with the first reports in 1960[4]. There are few randomized studies on their use in keloids, but broad medical consensus has led physicians to consider corticosteroid injections as first- or second-line therapy for keloids and hypertrophic scars[4]. Triamcinolone has been the most commonly used corticosteroid among the several employed for injection in scars[4].

Studies on keloid and scar treatment are complicated by several variables[5,6], including the lack of a suitable animal model[7] and the few objective methods to rate scars that could otherwise be readily available in physicians' offices and outpatient clinics[8]. In addition, scars on different sites of the body or caused by different mechanisms of injury are frequently combined in the studies, although the comparison of such lesions may not be appropriate.

This prospective, controlled, randomized, unblinded, single-center study aimed to compare the efficacy of silicone dressings versus triamcinolone injections versus both (combination treatment) on keloidal or hypertrophic median sternotomy scars.

PATIENTS AND METHODS

The study was approved by the Institutional Review Board of the Federal University of Minas Gerais and registered with the Brazil Platform (protocol number 06580513700005149). A detailed letter on potential study participants was sent to Cardiac Surgery Hospitals in Belo Horizonte, Minas Gerais State, Brazil, as well as to the Brazilian Society of Cardiology, Minas Gerais Regional Chapter.

1. Patient referral. Patients came to our service referred by the cardiology centers that received the invitation letter. Only patients who met the inclusion criteria were accepted for the study. During the first appointment, the study was explained to the patient, who signed a written informed consent form previously approved by the IRB. All patients received assurance that they would be able to follow with new treatment offered by the study's medical team after the last study appointment at six months, at no cost to the patient.

Inclusion criteria: age 18-80 years at the start of the study; male or female gender; patients who agreed to and signed written consent to participate in the study. Exclusion criteria: pregnancy, severe asthma that could lead to use of corticosteroids for longer than two months; patients who had used intralesional steroids or radiation to treat their keloids; and age under 18 or over 80 years. Only patients who had scars with pain and itching or that were red, raised, and with keloidal features (starting to grow outside the original surgical scar) were accepted for the study. Patients with scars that were not considered hypertrophic or with lesions that were shrinking were not enrolled in the study.

2. Study groups. A random table was generated before the study began. Each patient was randomly assigned to one of the three study arms: group 1. intralesional triamcinolone injections (20 mg/ml), performed once a month for 6 months (total of 6 injections); the injections were performed along the entire scar at 1 cm intervals, at approximately 1-2 mm from the scar's surface, with 0.05-0.1 ml per injection site; group 2. a combination group, combining triamcinolone injection and occlusive silicone dressing; group 3. occlusive silicone gel dressing, used 24 hours a day. Patients were advised to keep the silicone sheets on 24 hours a day, 7 days a week, removing the dressings every 7 days during their shower. The silicone sheets were then rinsed with water and left to dry on top of a glass surface for an hour, and then reapplied to the scar. The scar was washed once a week with soap and water during the shower.

3. Patient evaluation during clinical appointments. Each patient was evaluated in clinical appointments on day one, before receiving any treatments, and then once a month, by the same physician. Patients were asked to come to the hospital after removing the dressings at home. The Vancouver parameters were rated using the modified Vancouver Scar Scale [9,10]. An objective measurement of the pliability was then performed with a durometer (Rex Gauge, 1000, Rex Gauge Company, IL, USA), as described elsewhere [11]. The most hypertrophic area of the scar was chosen for evaluation, and that same area was evaluated in each of the monthly appointments. When two areas of the scar were considered clinically very severe and it was unfeasible to choose between them, the mean value for the two scars was used.

4. Silicone group. The silicone dressing (Medgel, Silimed, RJ, Brazil) was applied over the entire scar, as previously described[3]. Because the dressing is adherent but has no glue (it is not adhesive), it was attached with the help of microporous surgical tape covering the entire silicone dressing and extending 1 cm beyond the dressing on each side. The patient was instructed to keep the dressing in place for the next seven days, without removing it when showering. If patients performed intense physical exercise or felt itching or sweating on the treated area, they were instructed to remove the tape, rinse both the skin and the silicone sheet, and place the dressing back on 2-3 hours later. Patients received the physician's telephone number in order to contact the medical team whenever necessary. After seven days, the patient removed the dressing during the shower, rinsed both the dressing (with cold water) and the scar area, and replaced the dressing. According to the manufacturer's package insert, the product was expected to last 2 to 4 months. Since patients appeared for monthly appointments, the silicone dressing was replaced whenever it changed color, appeared dirty, or lost its adherent properties. After 3 months, if the dressing began to deteriorate and release small fragments, it was also replaced.

5. Triamcinolone injections. Triancil® (20 mg/ml, Apsen Laboratory) was administered in monthly injections along the entire scar at 1-centimeter intervals. An insulin needle was used, connected to a 1 ml insulin syringe, and a total volume of 0.05-0.1 ml was injected in each injection site. Areas that improved

over time did not receive subsequent injections. Patients that developed itching after the injections received oral prednisolone 20 mg, 4 hours prior to the next procedure.

6. Biopsy, immunohistochemistry, and confocal microscopy for collagen types I and VI: A 3 mm skin biopsy was performed on patients that agreed to the procedure (one patient from each group). Biopsies were performed on the same patient at baseline (before treatment) and at the 6-month appointment (last study day). The specimen was collected, rinsed with saline solution, and placed in a cold cryo-substitute solution (80% methanol/20% DMSO) in vials that were submersed in dry ice, as previously described (12). After deparaffinization and rehydration, three consecutive sections, 5 micrometers thick, were blocked for one hour with 1% bovine serum albumin (Vector Laboratories, Burlingame, CA) and incubated overnight at 4oC with a polyclonal primary antibody for collagen I or collagen VI at a dilution of 1:200 (Rockland Immunochemicals®, PA). On the following day, Alexa Fluor 488 conjugated goat anti-rabbit IgG was used as secondary antibody (Molecular Probes®, Eugene, OR) and cell nuclei were labelled with 4,6-diamidino-2-phenylindole (DAPI) (Molecular Probes®, Carlsbad, CA). The images were captured with a confocal laser scanning microscope (Zeiss 880META®, Oberkochen, Germany) at 16 bits and analyzed in the gray-scale range of 0-255 using Image Tool® 3.0 Software. Images were captured at 40X magnification and analyzed by an expert morphologist, trained in both immunohistochemistry and confocal skin collagen images, and who was also blind to the study groups.

Statistics. The data were submitted to a normality test and detected as non-parametric distribution. The three groups were compared using the Kruskal-Wallis test, and the evaluation from baseline to 6 months was performed with the Friedman test. Significance for all tests was $p < 0.05$.

RESULTS

Twelve patients who met the inclusion criteria were enrolled in the study, four in each group. Patients 1-14 were randomly assigned to the 3 study groups. At that point, group 1 had only 2 patients, so the last 2 patients enrolled in the study were assigned to group 1. All patients were seen monthly and completed the study. Groups 1 and 3 had 1 male and 3 female patients, while group 2 had 2 male and 2 female patients. 33.3% of the study patients were males, and 66.7% were females (Table 1. Patient Demographics). The keloids were located on the chest. The mechanism of injury that had led to keloid formation was cardiac surgery. Table 1 shows the study participants' demographics.

Vancouver Scar Scale (Table 2). According to the Vancouver Scar Scale, all the groups improved from baseline to 6 months ($p < 0.05$): Group 1 ($p = 0.002$), Group 2 ($p = 0.004$), and Group 3 ($p = 0.014$ - Graph 1). When the three groups are compared at each time point, groups 2 and 3 showed more improvement than group 1, mainly in terms of vascularity (at times 2, 4, and 5, there was a statistically significant difference between group 1, which had higher degrees of vascularity, and groups 2 and 3, with lower vascularity- Graph 2).

Pigmentation. Evaluation over time showed that group 2 improved significantly in the pigmentation parameter ($p = 0.042$) (Graph 3).

Scar height. When the three study groups were compared at each of the timepoints, group 1 showed the worst improvement at time 2, when compared to groups 2 and 3 ($p=0.036$). Analysis over time showed significant reduction in scar height in the three groups- group 1 ($p = 0.003$), group 2 ($p = 0.012$), and group 3 ($p = 0.047$) (Graph 4).

Durometer. From baseline to 6 months, group 1 ($p = 0.044$) and group 2 ($p = 0.023$) showed a significant decrease in the durometer grades, while no difference was seen in group 3. When the three groups were compared at each study time, no significant differences were observed (Graph 5).

Immunohistochemistry. Type I collagen. Although there were 4 patients in each group, only one patient from each group agreed to submit to skin biopsy. The 3-mm skin biopsy was performed before the treatment started and was repeated in the same patient at 6 months. Type I collagen was distributed throughout the dermis, with stronger expression seen in the upper dermis. When the scar was treated, type I collagen expression decreased throughout the dermis, mainly in deeper layers, and greater contrast was seen in treated scars in the upper and lower layers. Less variation was seen in untreated scars, suggesting that type VI collagen deposition may increase in deeper layers of untreated keloids (Figure 1). Type VI collagen. Type VI collagen distribution occurred throughout the dermis, following a similar distribution pattern to that seen in type I collagen. However, type VI collagen expression appeared to be stronger in the upper dermis of untreated scars, when compared to type I Collagen, and greater variation was seen between the upper and lower dermal layers (Figure 2).

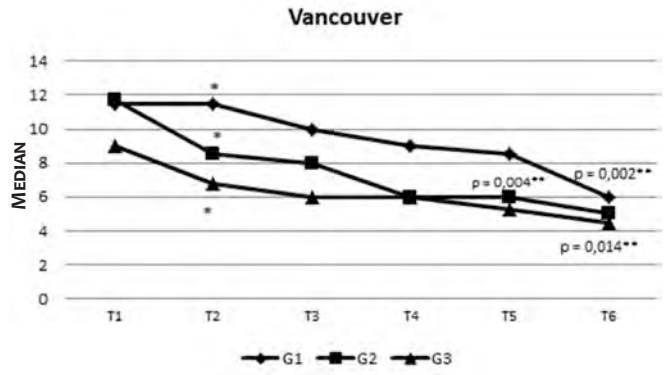
Table 1: Pacients' sociodemographic data

Sex	Age (years)	Study group	Evolution (months)
M	61	1	18
F	63	1	72
F	21	1	8
F	38	1	36
M	66	2	96
F	47	2	24
F	61	2	48
F	32	2	8
F	44	3	4
F	44	3	24
M	71	3	12
M	59	3	14

Groups 1 and 2 had 3 female patients and 1 male patient each, and group 3 had 2 female patients and 2 male patients. Age refers to the patient's age at the start of the study, while evolution refers to the number of months since the cardiac surgery with median sternotomy

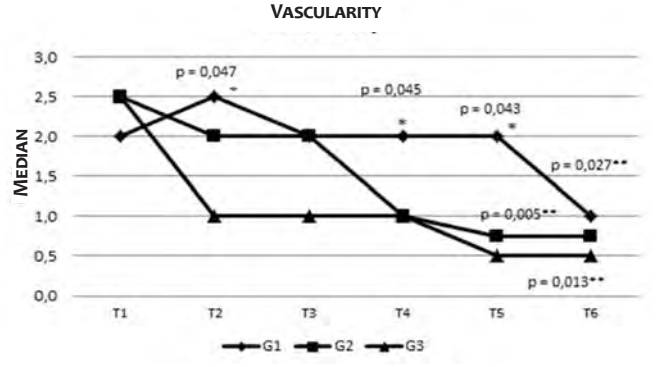
Table 2: VANCOUVER SCAR SCALE

Pliability	0	**Normal**
	1	Elastic
	2	Mobile
	3	Firm
	4	Adhered
Height	0	Normal
	1	1-2 mm
	2	3-4 mm
	3	5-6 mm
	4	>6 mm
Vascularity	0	Normal
	1	Pink
	2	Red
	3	Purple
Pigmentation	0	Normal
	1	Mild
	2	Moderate
	3	Severe



Groups 1, 2, and 3 showed significant improvement from baseline to time 6, according to the Vancouver Scar Scale ($p<0.05$)
* Difference between the groups at time 2
** Difference in the same group from baseline to 6 months.

Graph 1: Evaluation of study groups according to Vancouver Scar Scale

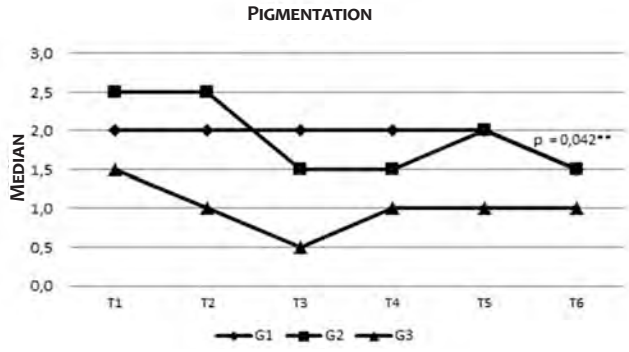


The three groups showed significant improvement in vascularity from T1 to T6. In the comparison of the group, groups 2 and 3 showed significantly better scores than group 1 at T2,T3,T4, and T5
*Difference between groups at times 2, 4, and 5
** Difference in same group at baseline and 6 months

Graph 2: Vascularity in study groups according to Vancouver scale

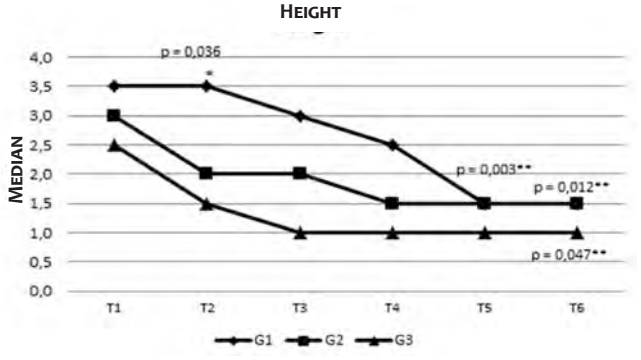
DISCUSSION

Silicone dressings improved scar pliability when applied to the scar tissue 12–24 hours a day for 6 months (3). The scar tissue became softer, allowing better diffusion of intralesional steroids (13). There is a lack of controlled studies in scars, comparing silicone dressings to other treatments. In some studies, other methods were associated, such as excision and triamcinolone injections (8, 13, 14, 15 e 16), thus making it difficult to evaluate the effect of the silicone itself (17). In order to address this issue, we designed a study with previously untreated patients who only used each study group's specific treatment. There is widespread agreement that silicone dressings promote hypertrophic scar/keloid improvement by increasing hydration and occlusion (3). Other possible mechanisms of action in the improvement of keloids with silicone include limiting skin stretching during healing (18) and increasing temperature, hydration, and oxygen tension (19). We have previously shown that occlusive dressings, including silicone and non-silicone sheets, lead to complete or partial improvement of physical parameters in scars and keloids. (3). The low cost and very low risk of side effects have led dermatologists to consider silicone and non-silicone dressings as



Pigmentation, one of the parameters of the Vancouver Scar Scale, improved with the association of the two treatments ($p = 0.042$), but at time 6 no significant difference between the 3 groups was observed.
* Difference in group 2, from baseline to time 6.

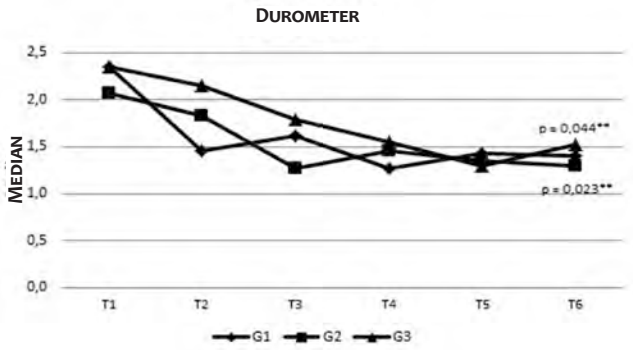
Graph 3: Pigmentation in the study groups



Height" according to Vancouver scale showed significant improvement in the 3 groups
*Difference between the study groups at time 2
** Difference in each group from baseline to 6 months.

Graph 4: "Height" according to the Vancouver scale

first-line treatment for keloids and hypertrophic scars (3). We believe that the protocol for silicone gel dressing can also positively impact the outcome, since we found that scars treated with silicone sheets applied 24 hours a day, 7 days a week (dressings were only removed once a week to wash the skin and scar area) showed better outcomes (data not shown).



Groups 1 and 2 showed significant decrease in durometer measurements from baseline to 6 months.

** Difference in each of the study groups from baseline to 6 months.

GRAPH 5: Evaluation with "durometer" over time in the study groups

Corticosteroids have been used since 1960 to treat keloids and scars (4), and triamcinolone is the most commonly used corticoid for this purpose (4). Corticosteroids can inhibit collagen synthesis by reducing inflammation and fibroblast proliferation and increasing hypoxia (20). Steroids also reduce plasma protease inhibitors, allowing collagen degradation (21). They also increase basic fibroblast growth factor (bFGF) and decrease transforming growth factor-β1 (TGF-β1) by dermal fibroblasts, endogenous vascular endothelial growth factor (VEGF), and insulin-like growth factor-1 (IL-1) (4). Roques & Teot (2008) suggest three mechanisms to explain how corticosteroids improve keloids: suppression of inflammation and cell migration; vasoconstriction; and antimitotic effect on keratinocytes and fibroblasts (4). The scar's response to intralesional steroids varies from 50% to 100%, with recurrence rates ranging from 9% to 50% (22). There is no consensus among clinicians regarding the dose, frequency, and duration of treatment. Adverse effects include hypopigmentation, skin and subcutaneous tissue atrophy, telangiectasias, ulcerations, and Cushing's syndrome (4). Robles et al. (2007) recommend triamcinolone acetonide at concentrations ranging from 10 to 40 mg/mL, in monthly injections (23). A review in 2016 evaluated the efficacy of corticosteroid injections in keloids and hypertrophic scars, comparing the technique

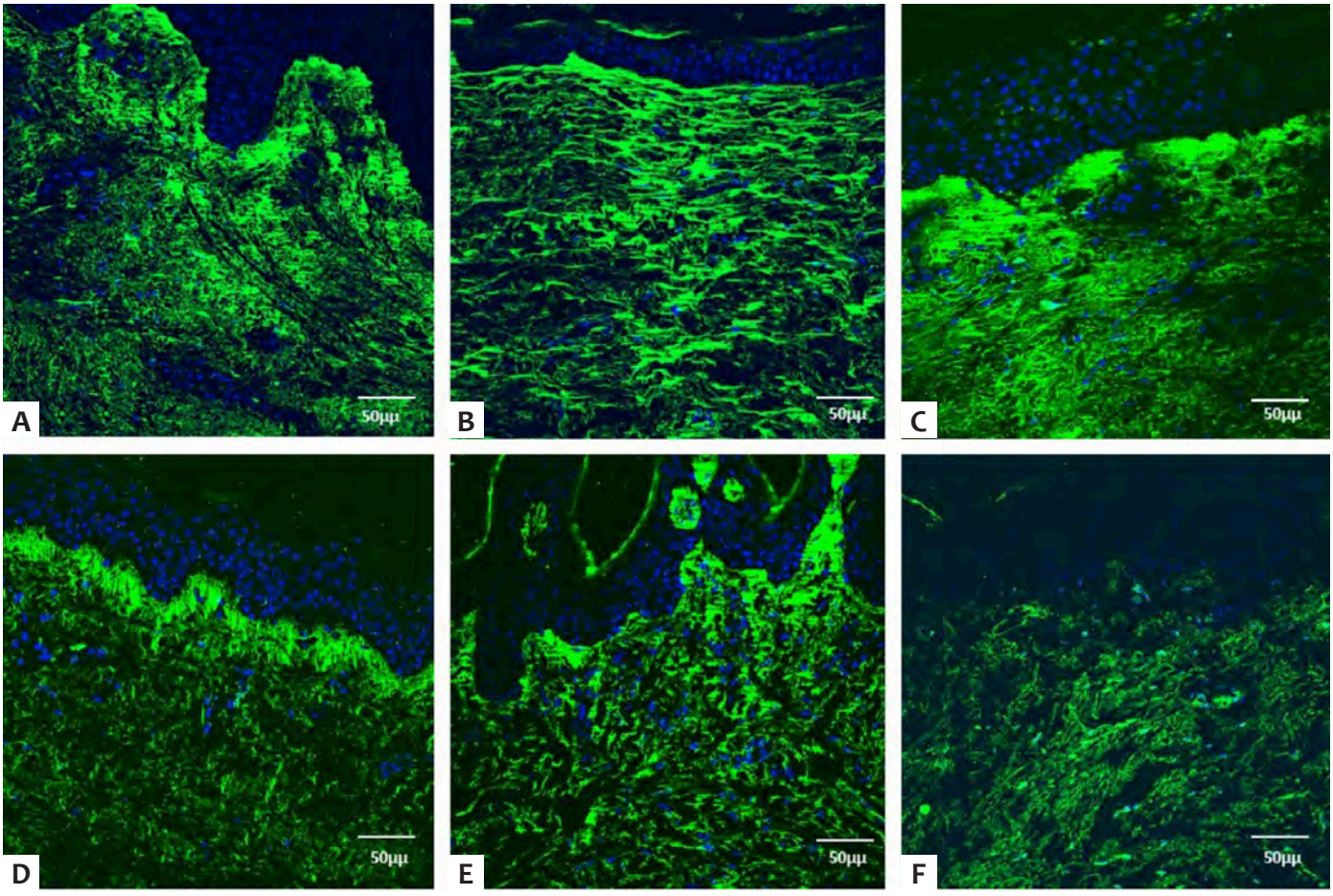


FIGURE 1: type I collagen in untreated scars (a,b,c) and treated scars (d,e,f). Immunohistochemistry and confocal microscopy of type 1 collagen in untreated scars (a,b,c) and treated scars (d,e,f). Group 1 (a,d) , Group 2 (b,e), and Group 3 (c,f). Collagen staining with AlexaFluor conjugate antibody. Nucleic staining with DAPI

to other treatment modalities such as silicone gel, verapamil, and antineoplastic drugs (24). Our study showed that triamcinolone injections alone were less effective in the initial treatment, as measured by vascularity. However, at 6 months, no significant differences were observed when lesions treated with triamcinolone were compared to silicone dressings. When triamcinolone injections were associated with silicone sheets, no significant improvements were identified in our study (although we call attention to the study's small sample size).

The Vancouver Scar Scale was the first attempt to standardize scar assessment by different observers. Pigmentation, pliability, height, and vascularity were scored, and the sum of the scores was higher in more hypertrophic scars (4). The Vancouver scale became a generally accepted clinical scar assessment tool in most scar treatment centers (5). Several attempts have been made to improve the scoring system, adding objectivity to scale parameters (4,6,7). In the current study, we added the durometer assessment. "Pliability", a term that refers to the elastic texture of the skin and scar, is one of its parameters. To assess pliability, the observer must touch the skin or scar surface, limiting its use only for clinical assessments (4). The durometer has been shown to adequately correlate with Vancouver pliability scores (11). We found that the durometer is affordable and easy to handle, due to its small size. Durometers have been used to assess the skin's hardness in leg ulcers, morphea, and scleroderma (25, 26).

Immunohistochemistry with confocal laser scanning microscopy has several advantages over scanning electron microscopy and conventional optical microscopy. Single tissue layer scanning eliminates the errors that occur in regular fluorescence microscopy as the result of variations in the thickness of histological sections. It allows for a precise evaluation of collagen distribution in skin layers and helps understand differences in expression among the various layers (12).

Type I collagen is a cellular matrix protein dermal collagen seen in the dermis of normal skin and scars. We have previously shown that its expression is increased in more hypertrophic scars (12, 27) when compared to normal skin and non-hypertrophic scars. Non-hypertrophic scars display type I collagen expression that is more similar to normal skin. In the present study, notwithstanding the small sample size, we also found that treated scars (less hypertrophic) are prone to decreasing type I collagen expression.

Type VI collagen is a key regulator of dermal matrix assembly, composition, and fibroblast behavior and may play an important role in wound healing and tissue regeneration (28). Its

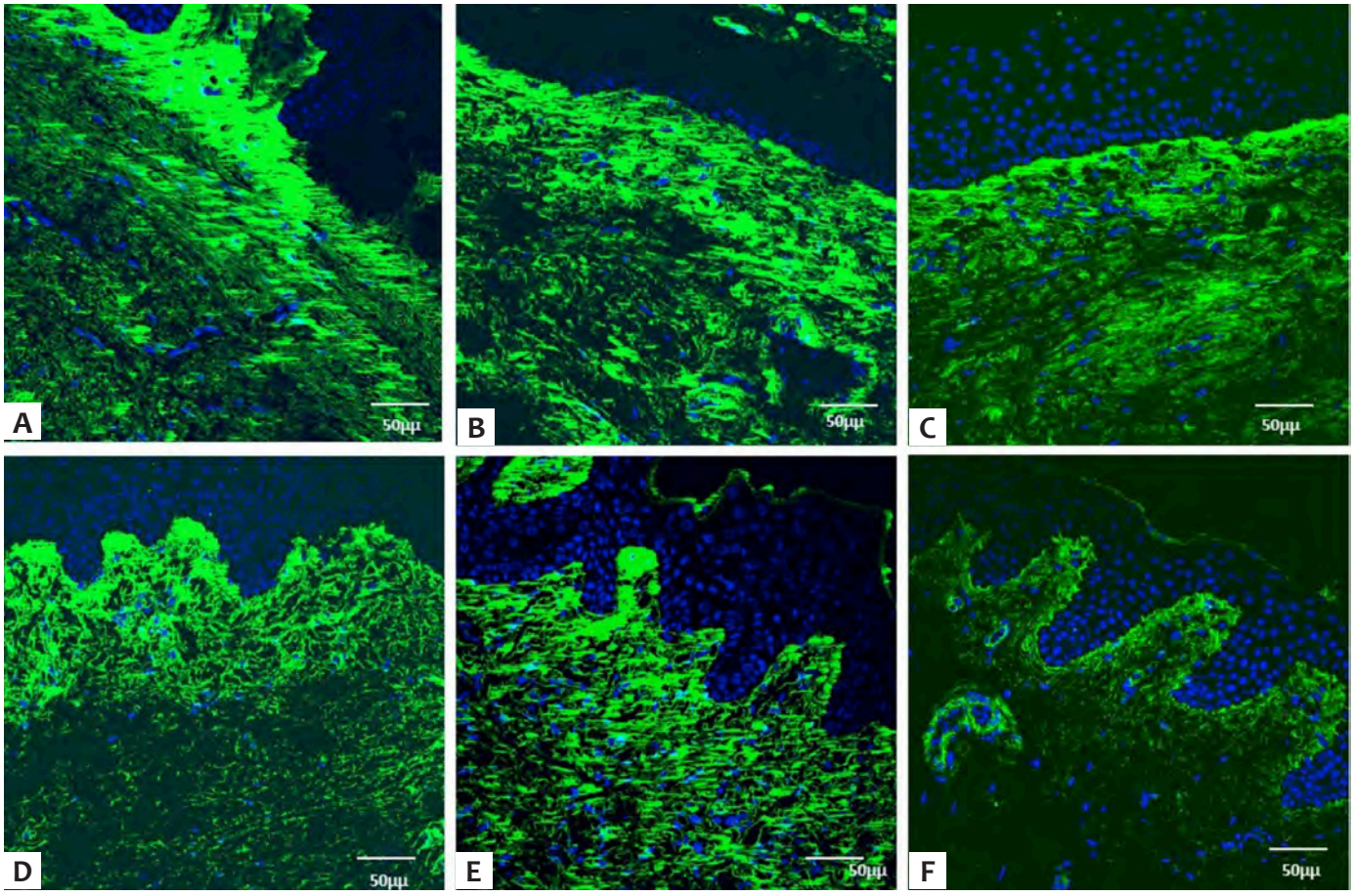


Figure 2: Type 1 collagen in untreated scars (a,b,c) and treated scars (d,e,f). Immunohistochemistry and confocal microscopy of type VI collagen in untreated scars (a,b,c) and treated scar (d,e,f). Group 1 (a,d) , Group 2 (b,e), and Group 3 (c,f). Collagen staining with AlexaFluor conjugate antibody. Nucleic staining with DAPI

distribution is similar to collagen types I and III, and it has been shown to be located in the upper dermis of keloids (29). Our study found stronger type VI collagen staining in the upper dermis of the scar. We also showed that untreated lesions displayed increased type VI collagen when compared to the same scar after treatment. Although our study was limited by the small number of patients, the decreased expression of type VI collagen appears to correlate with the overall improvement of the keloid (Figure 2). To our knowledge, the is the first study to date that has shown type VI collagen expression in untreated and treated scars using immunohistochemistry staining and confocal microscopy. New studies with larger numbers of patients are needed to confirm this result.

Variables that act as confounding factors in scar and keloid studies include: the lack of prospective, randomized study designs; subjective methods for scar evaluation; and the heterogeneity of scars caused by different mechanisms of injury and in different anatomical regions, and that have been grouped together for comparison. Many of the studies include scars previously treated with drugs and methods with prolonged effects, such as corticosteroids, antineoplastic drugs, or radiotherapy (3, 11). The present study attempted to rule out such potential confounders by including only patients with pre-sternal scars, all caused by the same mechanism of injury (cardiac surgery). Patients who had received previous treatments were excluded. Because we aimed to adhere to very strict inclusion criteria, few patients were enrolled in the study, which we consider a limitation. However, we feel that the study will provide guidance for a future and much larger multicenter study. We call attention to the difficulties in obtaining larger groups of patients with scars caused by the same mechanism of injury and on the same body area, The motivated the creation of GREMCIQ- the Brazilian Group for Multicenter Studies of Keloids and Hypertrophic Scars. The group includes dermatologists from different regions of Brazil, with the main goal promoting collaboration in the development of multicenter studies to improve the understanding of treatments for keloids and hypertrophic scars in a highly mixed racial population, prone to the development of such lesions.

Acknowledgements

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The study was conducted at the Dermatology Outpatient Clinic at the University Hospital of the Federal University of Minas Gerais (UFMG), initial home to the Outpatient Clinic for Treatment of Keloids and Hypertrophic Scars. The clinic has now moved to Hospital Mario Penna, Belo Horizonte, MG. Immunohistochemistry and confocal microscopy were performed at CEMEL (Electronic Microscopy Center) of the ICB (Institute of Biological Sciences), UFMG. The study did not receive any financial support.

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Original Articles

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Nasal reconstruction after Mohs micrographic surgery: analysis of 208 cases

Nasal reconstruction after Mohs micrographic surgery: analysis of 208 cases

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ABSTRACT

Introduction: The nose is frequently affected by cutaneous carcinomas. Due to its functional and cosmetic importance, tumors on this location are preferably treated by Mohs micrographic surgery, which provides the highest cure rates. For repairing of surgical defects several options are available, including healing by second intention, primary closure, skin grafts, and flaps. In certain cases, one should consider a combination of methods.
Objective: To describe the authors' experience in nasal reconstruction after Mohs surgery and to assess if the number of involved subunits influenced the use of combined repairs.
Methods: Retrospective study of consecutive cases submitted to Mohs surgery and nasal reconstruction by one of the authors during a 3-year period.
Results: 208 cases were included, and the most common repair method were flaps (n = 82). Combined methods were performed in 44/154 (29%) cases with involvement of only one nasal anatomical subunit and 29/54 (54%) cases with multiple nasal subunits involved.
Conclusions: The dermatologic surgeon should be familiar with different options for nasal reconstruction. The combination of repair methods was often performed, mainly for wounds that affected more than one nasal subunit.
Keywords: Carcinoma, basal cell; Mohs surgery; Nose neoplasms; Surgical flaps

RESUMO

Introdução*: O nariz é frequentemente acometido por carcinomas cutâneos. Devido à importância funcional e estética, tem como primeira indicação a cirurgia micrográfica de Mohs, método com a maior taxa de cura. Para reparo das feridas operatórias, inúmeras opções estão disponíveis incluindo cicatrização por segunda intenção, fechamento primário, enxertos cutâneos e retalhos. Em certos casos, deve-se considerar a combinação de métodos.*
Objetivo: *Descrever a experiência dos autores na reconstrução nasal após cirurgia de Mohs e avaliar se o número de subunidades anatômicas acometidas influenciou no uso de métodos combinados de reparo.*
Métodos: *Estudo retrospectivo de casos consecutivos submetidos à cirurgia de Mohs e à reconstrução nasal por um dos autores, num período de três anos.*
Resultados: *Foram incluídos 208 casos e o método de reparo mais comum foram os retalhos (n=82). A combinação de métodos foi utilizada em 44/154 (29%) casos com acometimento de apenas uma subunidade anatômica nasal e em 29/54 (54%) casos com múltiplas subunidades nasais envolvidas.*
Conclusões: *O cirurgião dermatológico deve se familiarizar com as diferentes opções de reconstrução nasal. A combinação de métodos de reparo foi frequentemente utilizada, principalmente para feridas com acometimento de mais do que uma subunidade nasal.*
Palavras-chave: *Carcinoma basocelular; Cirurgia de Mohs; Enxerto; Neoplasias nasais; Retalhos cirúrgicos*

INTRODUCTION

The nose is one of the facial units most frequently affected by carcinomas of the skin.[1] Due to the aesthetic and especially functional importance of the nose, it is crucial to offer patients treatments with lower chances of recurrence. Thus, various guidelines recommend Mohs micrographic surgery (MMS) for cutaneous carcinomas located in this region.[2-4] The technique consists of 100% assessment of the surgical margins, compared to examination of around 1% in the conventional excision.[5,6] This complete assessment of the margins provided by MMS leads to the highest cure rate in the treatment of carcinomas, and its indication is thus important in noble areas of the face such as the nose.[7]

Even with MMS, which preserves healthy tissue, many nasal surgical defects are challenging because of the complex local anatomy, with its peculiar three-dimensionality. The priority of nasal restoration should be functional before aesthetic, but the latter should never be overlooked, since postoperative nasal deformities can have significant psychological impact.[8] It is thus essential to combine both aspects, functional and aesthetic.

The repair of nasal surgical defects should consider their diameter and depth, the availability of adjacent skin, and the patient's expectations[9,10] Numerous options are available, including healing by secondary intention, primary closure, skin grafts, and flaps. A combination of methods should be considered in certain cases.

One of the main factors that influences the choice of reconstruction method is the availability of skin adjacent to the wound. On the nose, this availability is limited in the lower third, formed by the tip, ala, columella, and soft triangles. In the upper thirds (nasal sidewalls and dorsum), the skin usually tends to be less sebaceous and more elastic.

The study aimed to describe the authors' experience with nasal reconstruction after Mohs micrographic surgery and to assess whether the number of affected anatomical subunits influenced the use of combined methods for repair.

METHODS

This was a retrospective study of consecutive cases submitted to MMS and nasal reconstruction by one of the authors (FBC) from January 2017 to December 2019. The cases were from the private practice and the university hospital where the authors work. The study was approved by the local Institutional Review Board.

Nearly all of the surgeries were performed under local anesthesia with lidocaine and bupivacaine with vasoconstrictor. When necessary, nerve block (external nasal branch of the ethmoidal nerve, supratrochlear, or infraorbital) supplemented the local anesthesia. For larger reconstructions or more anxious patients, oral benzodiazepine (lorazepam) was associated at a dose of 1mg. Antibiotic prophylaxis is a controversial issue[11-13], and the authors follow the recommendation by Wright *et al.*, which consists of administering 2g of cephalexin 30 minutes before surgery in cases with higher likelyhood of requiring nasal flaps and/or grafts or for patient's reasons (orthopedic prostheses, immunosuppression, prosthetic heart valves).[14] Postoperative antibiotic (cephalexin 500mg every six hours for seven days) was prescribed after complex surgeries, long duration or when cartilage graft was required.

Data analysis included a review of the photographic documentation and the following data: age, gender, Fitzpatrick skin phototype, tumor characteristics, defect size and number of anatomical subunits involved, number of MMS stages, reconstruction performed, use of antiplatelet agents or anticoagulants, smoking, and postoperative complications.

The nasal subunits were divided into dorsum and nasal sidewalls (upper thirds) and tip, ala, columella, and soft triangles (lower nasal third).[15] The reconstruction methods were divided into healing by secondary intention, primary closure, flaps, or graft. When more than one method was used, it was reffered as combined reconstruction. For analysis of the repair methods, we only considered the ones for closure of the nasal subunits. Methods used in adjacent subunits (cheek, for example) were not analyzed together, to avoid biases.

Complications were divided into two groups. Short-term complications were defined as bleeding that required reintervention, hematoma, infection, dehiscence, and flap/graft necrosis (partial or total). Long-term complications were defined as easily noticeable anatomical distortion (e.g., retraction of the nasal rim) and nasal obstruction.

RESULTS

The study included 208 cases from 190 patients. Two other patients were excluded, since they were referred to plastic surgery for reconstruction after MMS. Table 1 shows the demographic and surgical data.

The most primarily affected nasal subunits were the nasal sidewalls (n=75), followed by nasal tip (n = 52), dorsum (n = 45), and ala (n = 36) (Figure 1). In 154 cases, only one nasal subunit was involved, whereas in 54 two or more subunits were affected. In 15 cases, the wound extended to other subunits of the face (cheek=12, apical triangle=1, upper cutaneous lip=1, and eyelid=1). In such cases, the subunits beyond the nose were restored by primary closure or (n=8) by secondary intention (n=7).

Graph 1 shows the reconstruction methods performed. For the nasal dorsum, primary closure was the most frequently used. Flaps were the most common for the nasal sidewalls and tip, and grafts for the nasal ala. Regarding the flaps, in 82 cases they were the main repair method: rotation (n=21), island pedicle (n=15), transposition (n=14), advancement (n=12), island with lateral pedicle of the nasalis muscle (n=8), interpolation (n=6), and hinge (n=6). Two patients underwent surgical revision. One because of webbing on the inner canthus, treated with Z-plasty; and the other for thinning the flap. In four cases, intralesional steroids were was used with satisfactory results for treatment of "trapdoor".

Among the 154 cases with involvement of only one nasal subunit, 110 (71%) were restored with a single method and 44 (29%) with combined methods. Among the cases with multiple nasal subunits involved (n=54), in 29 (54%) a combination of methods was used for closure (Graph 2).

TABLE 1: DEMOGRAPH AND SURGICAL DATA

Age (years)	Gender	Fitzpatrick phototype	Smoker	Antiplatelet agents or anticoagulants
Mean, 65	121 women	I:3	20	16: Salicylic acid
36 to 91	69 men	II:91		8: clopidogrel
		III:93		
		IV:3		
Tumors	**Primary or recurrent**	**Anesthesia**	**Mean defect size (mm)**	**Number of stages**
197 BCCs	180 primary	Local: 201	11 x 9 (lower 1/3)	1.6 (1 to 6)
9 SCCs	25 recurrent	Local + lorazepam: 3	13 x 11 (upper 2/3)	
1 SCC *in situ*	3 inc. excised	Local + IV sedation: 4	From 4 x 3 to 40 x 35	
1 basosquamous carcinoma				

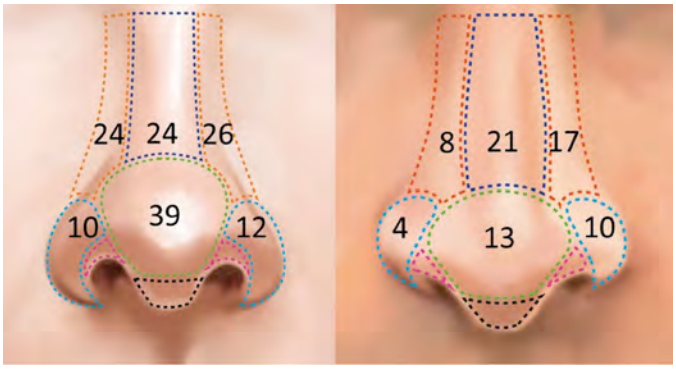
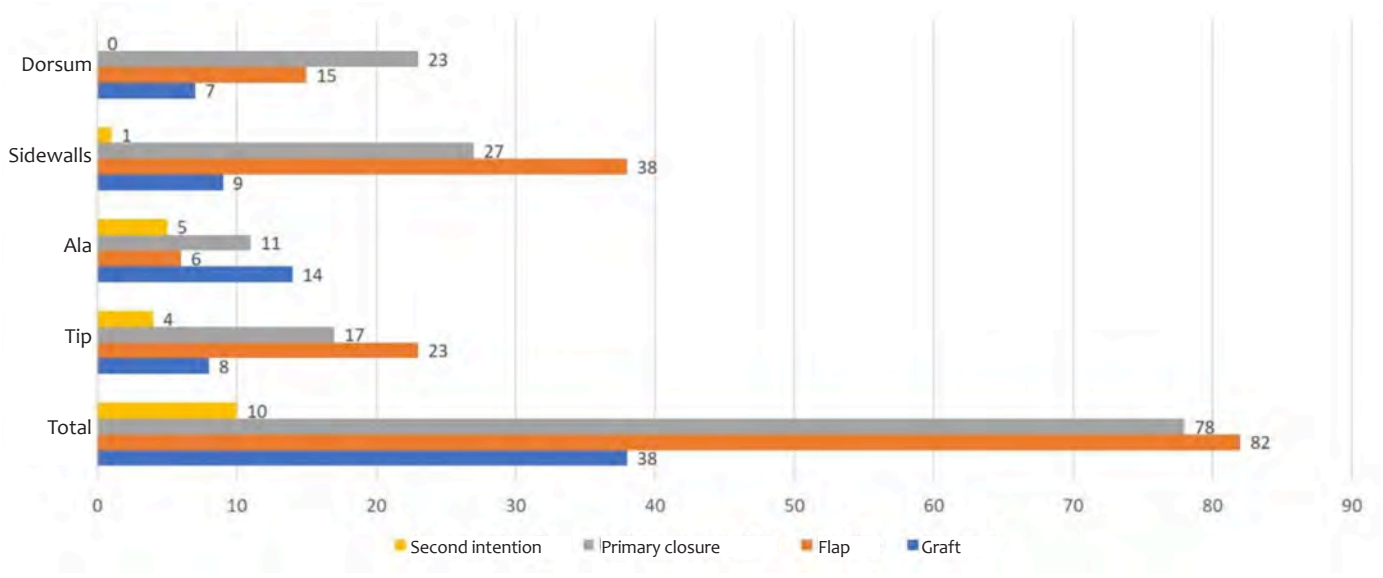


FIGURE 1: Location of tumors in women and men.
The main affected subunit was considered. If a tumor affected the tip and dorsum, for example, the subunit with the predominant involvement was considered.
Nasal subunits: tip (green), ala (light blue), soft triangles (pink), columella (black), sidewalls (orange), and dorsum (dark blue).

Pre- and postoperative prophylactic antibiotics were used in 104 and 41 cases, respectively. Complications occurred in 6.2% (n=13) of the cases, 12 were short-term and one was long-term. The most common complications were infection (n=4) and partial graft necrosis (n=4), followed by partial flap necrosis (n=3), dehiscence (n=1), and nasal valve disfunction (n=1). Infections were treated with oral antibiotics and healed uneventfully. Partial flap or graft necrosis were managed with local wound care. The patient that presented dehiscence, after early removal of the sutures, healed by secondary intention. The case of nasal valve disfunction due to inadequate flap design evolved with partial improvement and refused surgical revision.

DISCUSSION

Similarly to previous publications, the current study demonstrated the variety of available options for nasal reconstruction and the frequent need for flaps and grafts, even on the upper thirds of the nose.[16-19] It also showed that defects involving



*All the grafts were full-thickness

GRAPH 1: Main reconstruction method used according to subunits involved. For this analysis, in cases of combined closure, the main method was considered (the method that restored most of the defect).

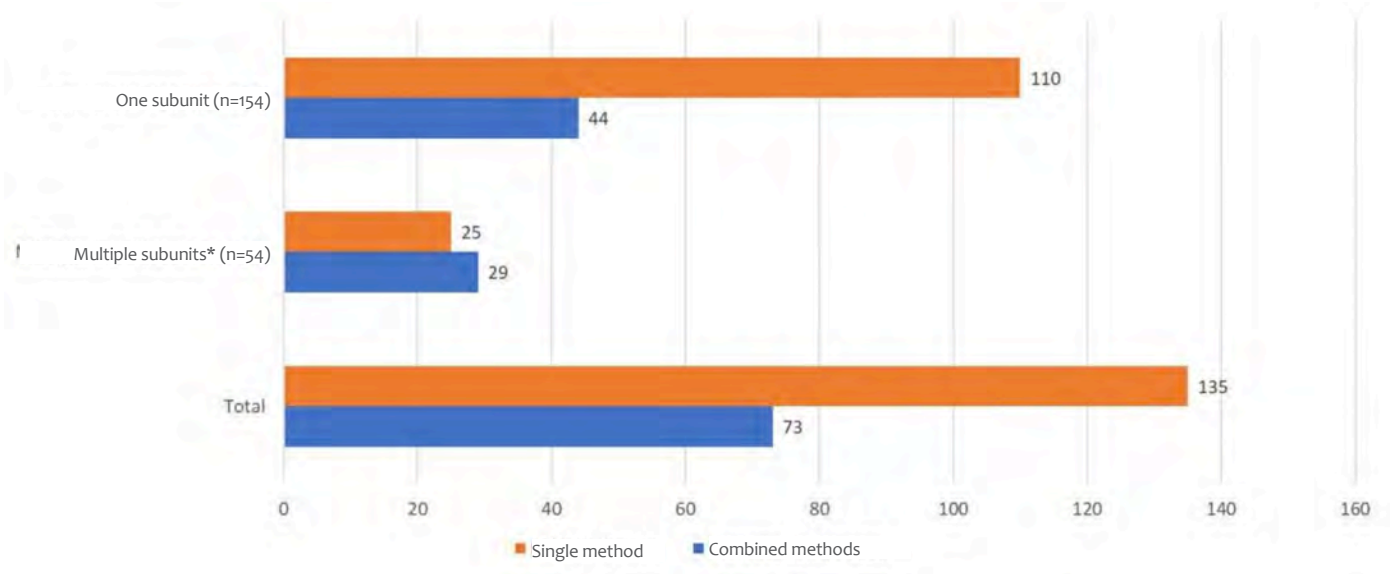
multiple nasal subunits were more often repaired with a combination of methods. This is especially true for defects involving the nasal ala and sidewall, where preservation of the alar sulcus is essential for facial symmetry (Figure 2).[20,21]

The repair choice varied according to the number and to nasal subunits involved. Similarly to previous reports, flaps were the most frequent reconstruction method.[17,22]

In a study that compared the outcomes of flaps and grafts for nasal restoration, the authors showed that well-designed flaps were more likely to result in superior cosmetic outcome.[23]

The nasal dorsum, due to the greater elasticity of adjacent areas (glabella and nasal sidewalls), was restored with primary closure or flap in 85% of cases. Figure 3 illustrates an excellent option of an advancement flap for this site, also known as the "east-west flap".[24] When performing a vertical primary closure on the nasal dorsum, the standing cones should be long to reduce the risk of uneven levels between the sutured area and upper and lower adjacent areas.[25] Although hard to notice from a front view this unevenness is easily noticed from side view.

For the nasal sidewall, flaps and primary closure were the most frequently used, a finding consistent with the literature.[17,26] Figure 2 illustrates a combined repair for a defect affecting multiple subunits, the main one the left nasal sidewall.



*Number of nasal subunits involved/cases: 2/40, 3/11, 4/3

Graph 2: Number of nasal subunits involved and reconstruction methods

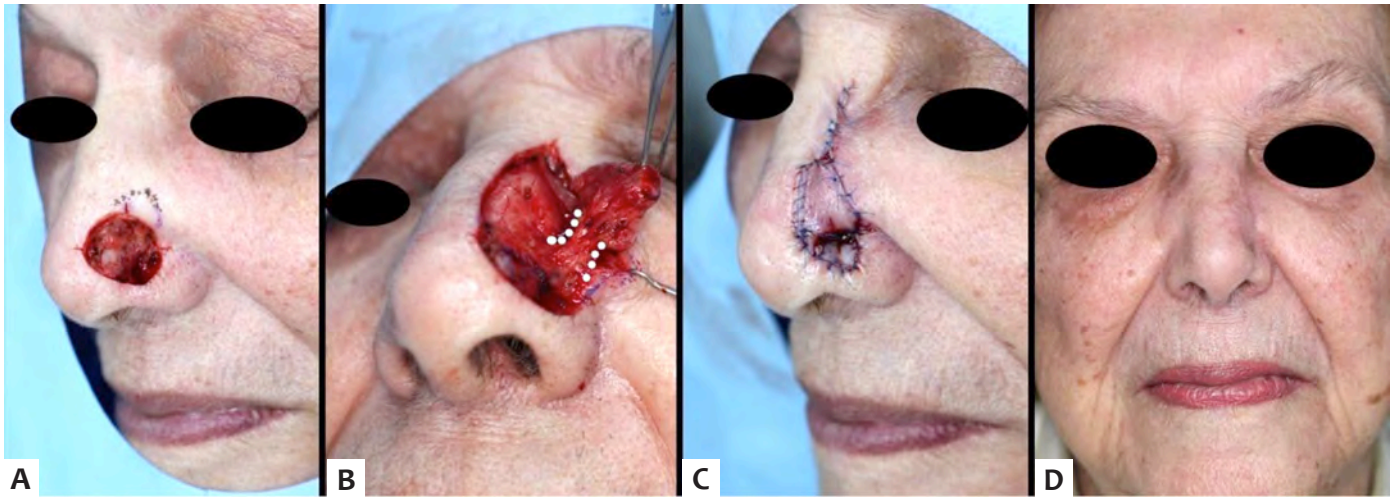


Figure 2: Combination of methods: island pedicle flap based on the nasalis muscle ("nasalis sling flap"), skin graft, and secondary intention
A) Surgical defect with involvement of nasal sidewall, ala, dorsum, and tip; **B)** Flap undermined. Unlike the regular island pedicle flap, this flap has a laterally based pedicle. (dotted white line). The flap is undermined in two distinct planes: supraperichondrial from the medial incision and subdermal from the lateral incision; **C)** Immediate postoperative view. The flap repaired the sidewall, dorsum, and tip (slightly involved). The nasal ala was restored with a skin graft harvested from the upper portion of the flap to avoid another donor area. The alar sulcus was left to heal by secondary intention to recreate its concavity; **D)** Two months postoperative, front view. Note recreation of alar sulcus and maintenance of nasal symmetry.

For flaps that recruit tissue from the cheek, two details deserve attention. The first is the maintenance of the nasofacial sulcus, especially when using lateral advancement flaps. This can be performed by fixing the deep portion of the flap on the nasofacial sulcus. Another detail is to adequately thin island pedicle flaps, since the nasal sidewall is much thinner than the cheek.

For the nasal tip, flaps and primary closure were the most common repair method. Among the flaps, the rotation was the most frequently performed. It allows incisions to be hidden between subunits (sidewall and dorsum, or nasofacial sulcus). The disadvantage is that this flap requires long incisions and significant undermining for adequate mobility and avoidance of nasal tip distortion. Another frequently used option was a variation of the Burow's graft, which consists on the combination of primary closure and a hinge flap and graft (both from the Burow's triangle)[27], similar to the method illustrated in figure 4.

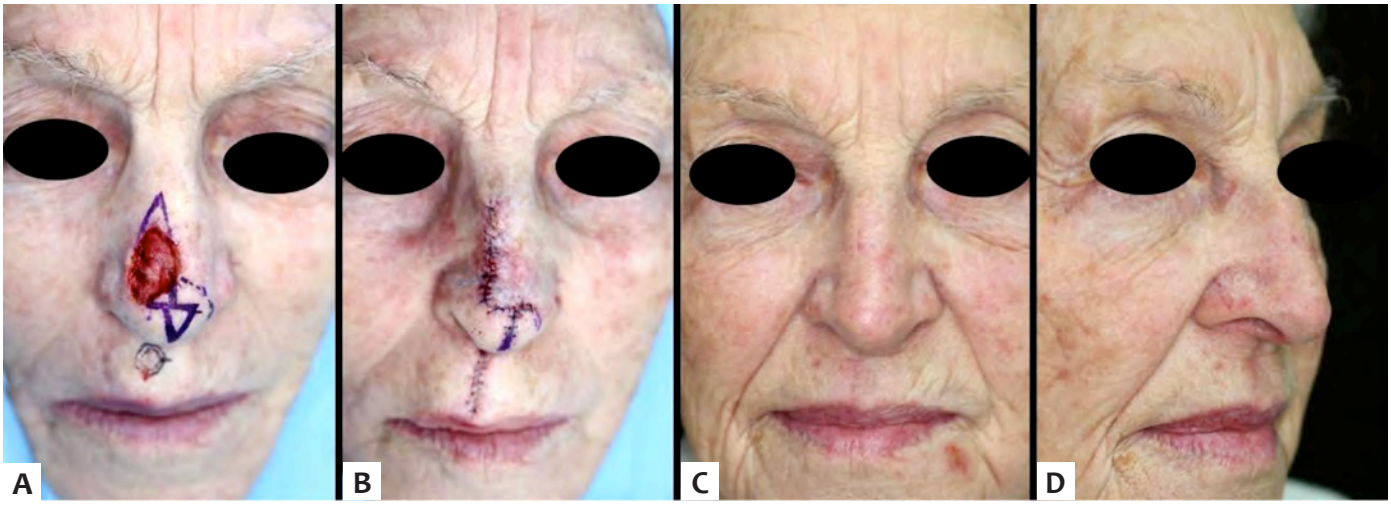


Figure 3: Unilateral advancement flap. **A)** Surgical defect involving nasal dorsum and tip. Flap design. It is important to remove "leftover" skin for adequate coaptation of surgical borders. This flap is also known as "east-west flap"; **B)** Immediate postoperative view; **C)** Two and a half months postoperative, front; **D)** Oblique view.

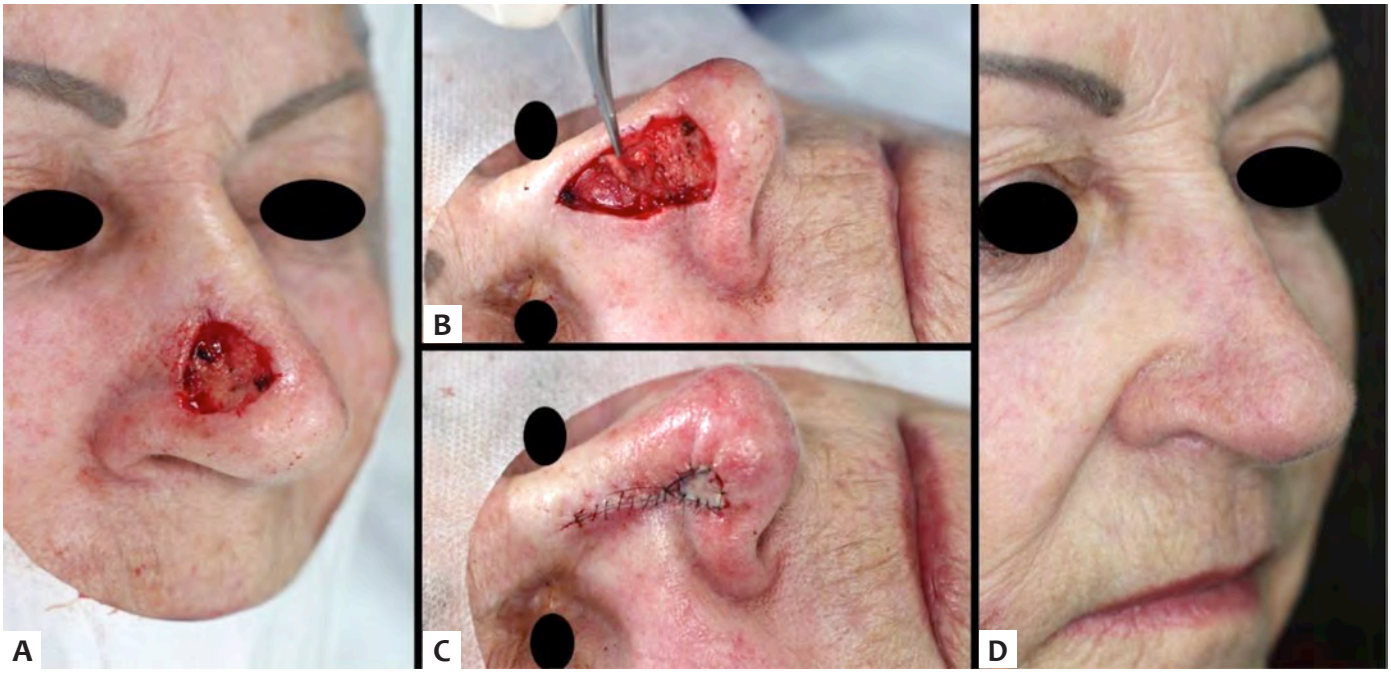


Figure 4: Primary closure combined with hinge flap and skin graft. A) Surgical defect with involvement of multiple subunits; B) 180-degree movement of hinge flap after de-epithelization (skin from the "de-epithelization" was used as graft); C) Immediate postoperative view. Defect restored with combined methods: primary closure for the upper third (sidewall and dorsum) and hinge flap with skin graft the for lower third (ala to tip transition); D) Two months postoperative

For extensive and deep defects of the nasal tip (in some cases with involvement of the dorsum), the paramedian forehead flap was performed (Figure 5), allowing adequate restoration of the nasal anatomy, as described in the literature.[9,28-30]

The nasal ala was the only subunit where graft was the main repair method despite numerous described flaps from the ala itself.[31,32] Because of the lack of support and the fact that the ala is a free margin, any minimal flaw when designing flaps from the ala itself can cause local distortion. For this reason, this author usually prefers grafts for small defects [33] and secondary intention when the alar sulcus is involved, or a combination of both (Figure 6). Primary closure can be useful for small alar defects, mainly those located on the medial portion of the ala adjacent to the tip. On the central or lateral portion, even small primary closures can cause collapse because of the vector that "pushes the ala inward". In the current study, secondary intention was one of

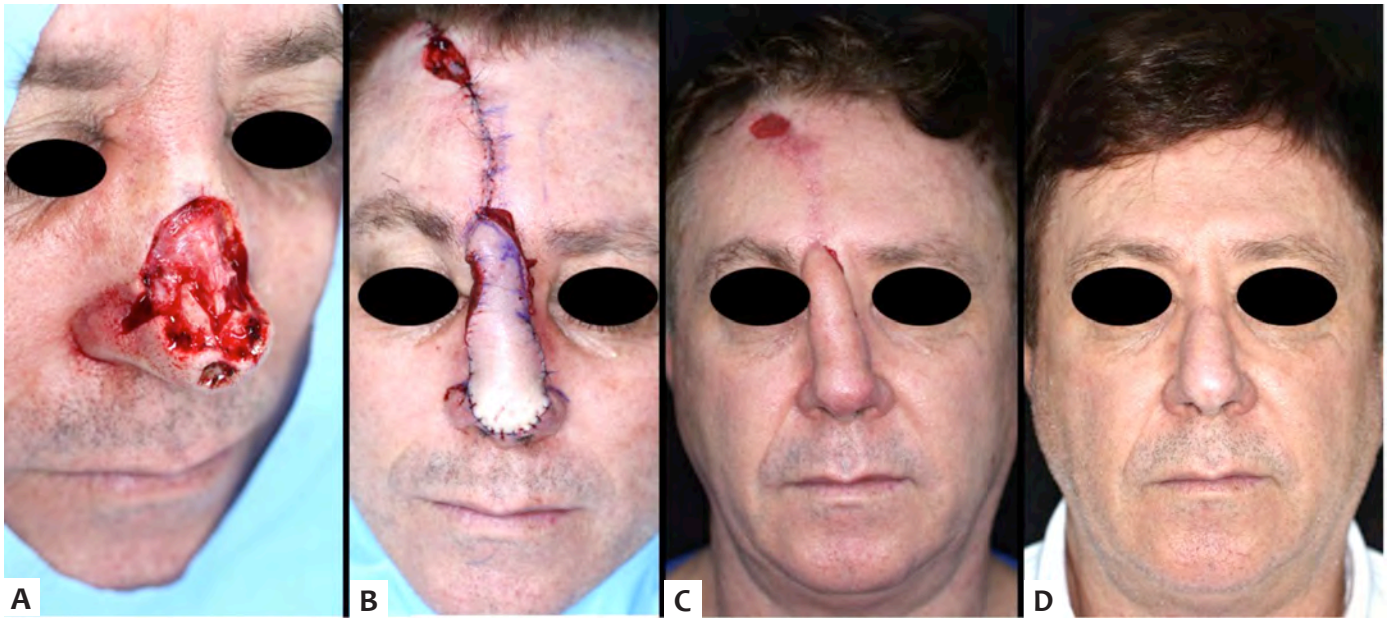


Figure 5: Paramedian forehead flap. **A)** Surgical defect after removal of a recurrent infiltrative BCC (treated twice with conventional excision in another institution) on the nasal dorsum and tip and a small primary BCC on the nasal tip. The defect area that affected the right inferior nasal sidewall and ala was partially closed primarily. Nasal dorsum and tip restored with paramedian forehead flap. Since the amount of cartilage removed was relatively small, the cartilages were reapproximated and no cartilage graft was used; **B)** Immediate postoperative, first stage. Donor area was partially closed and the rest left to heal by secondary intention. Note that the remaining of the nasal tip subunit was removed to camouflage the suture lines between the subunits; **C)** Preoperative view prior to second stage, performed after three weeks; **D)** Nine months postoperative with restoration of nasal anatomy. Incisions camouflaged between nasal subunits

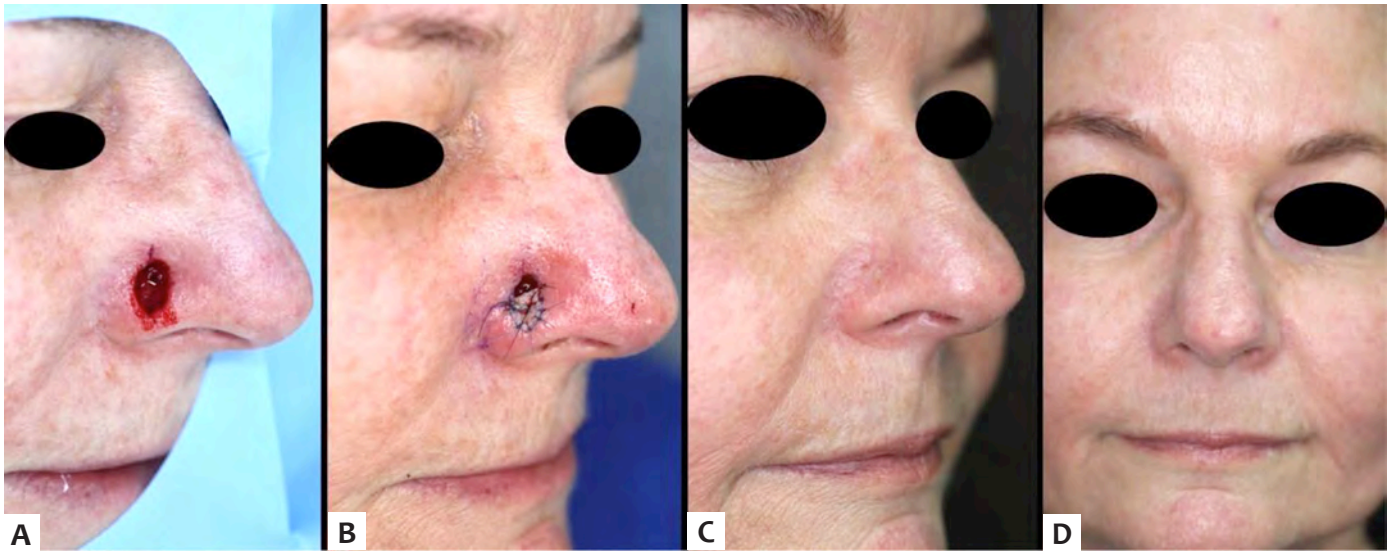


Figure 6: Graft combined with secondary intention. A) Surgical defect involving nasal ala and alar sulcus; B) Immediate postoperative view. Ala restored with a preauricular full-thickess skin graft. Alar sulcus left to heal by secondary intention; C) Two months postoperative oblique view; D) Front view. Note symmetry of alar sulci

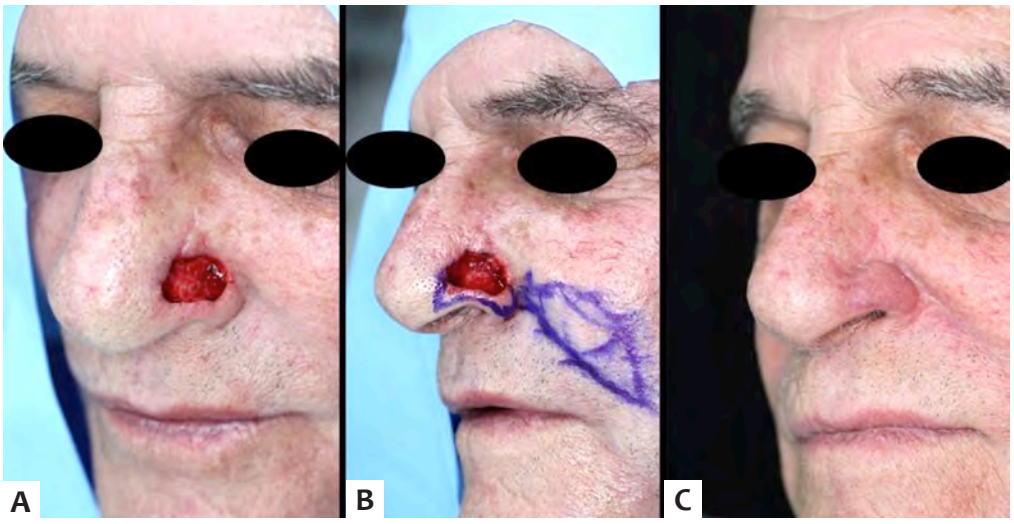


Figure 7: Nasolabial interpolation flap. A) Surgical defect on the left nasal ala with slight involvement of the inferior nasal sidewall and cheek. The patient was referred for MMS after excision with positive margins. Adjacent to upper portion of wound, note remaining area of a prior island pedicle flap, which was subsequently removed; B) Flap design. The template was based on the contralateral ala and did not include the defect area involving the nasal sidewall. Ideally, the flap pedicle should be longer, however, to avoid transferring beard follicles to the nose, the pedicle was shorter in this case (which limits the flap mobility). Although not shown in the images, a cartilage graft was used to ensure patency; C) Seven months postoperative with restoration of the nasal ala convexity and preservation of the alar sulcus.

the repair methods in 50% of the defects that involved the ala to some extent. The areas left to heal by secondary intention were mostly adjacent to the alar sulcus, a well-established practice in the literature.[34] Single-stage transposition flaps tend to obliterate the alar sulcus, causing easily noticeable asymmetry. Therefore, in cases with extensive involvement of the ala, the nasolabial interpolation flap (with cartilage graft) was performed (Figure 7). The technique requires two stages, however it allows recreating the entire alar subunit, besides preserving the alar sulcus.[28,35,36]

Almost all the surgeries (97%) were performed under local anesthesia, which is consistent with the literature from the United States, where MMS is performed on a large scale and only on extremely rare occasions under sedation.[37-39] Local anesthesia is the safest method for the patient, since MMS can take hours.[5,39-42] It is essential to use established techniques to reduce discomfort from local anesthesia on every patient.

One limitation of the current study is its retrospective design. However, the data from each surgery were uploaded into a database immediately after the procedure. Long-term data were uploaded after follow-up visits. These measures minimize possible retrospective study biases. Another limitation is that the study is based on a surgeon's preference, which can vary significantly, as reported by Alam et al. [43]

Finally, the authors are not proponents of cookbook formulas such as "defects up to 1.5cm on the nasal tip should be closed with a bilobed flap" etc.[44] The authors recommend careful evaluation of each defect and each nose. Same size defects on different nasal tips can be repaired by completely different methods according to local characteristics.[45] Therefore, more important than memorizing algorithms is to become familiar with different repair methods and flap biomechanics. This does not mean that surgeons should always do a distinct reconstruction for every case, but that they have a reasonable range of options.

CONCLUSION

Dermatologic surgeons should be familiar with the different options for nasal reconstruction. The combination of repair methods was frequently performed, mainly for defects involving more than one nasal subunit.

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Efficacy assessment of hair ampoule containing human hair follicle stem cells in hair loss reduction in women with androgenetic alopecia

Avaliação da eficácia de ampola capilar contendo células-tronco do folículo piloso humano na redução da perda capilar em mulheres acometidas por alopecia androgenética

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ABSTRACT

Introduction: Androgenetic alopecia is characterized by the thinning and progressive hair loss due to the action of androgen hormones, causing the miniaturization of follicles and altering hair cycle.

Objective: To assess the efficacy of a topical hair ampoule containing human follicle stem cells, in women with androgenetic alopecia.

Methods: We used phototrichogram and image analysis to determine investigational product's efficacy compared to placebo after four months of treatment.

Results: There was significant increase in the percentage of anagen hair (34.99%) and a decrease in the percentage of telogen hair (16.59%) for the treated group, what did not occur for the placebo group. There was significant increase in the scalp coverage for the treated participants after four months of product use (33.6%).

Conclusions: The topical investigational treatment was effective to improve hair loss in female androgenetic alopecia after four months of treatment.

Keywords: Alopecia; Hair; Clinical Trial; Hair Preparations

RESUMO

***Introdução**: A alopecia androgenética caracteriza-se pelo afinamento e perda progressiva dos fios de cabelo decorrentes da ação dos hormônios andrógenos, causando a miniaturização dos folículos e diminuição do tempo de duração do ciclo capilar.*

***Objetivo:** Avaliar a eficácia de ampola tópica capilar contendo células-tronco do folículo piloso humano em mulheres com alopecia androgenética.*

***Métodos:** Utilizou-se fototricograma e método de análise de imagem por cobertura para determinar a eficácia do produto investigacional comparado ao placebo após quatro meses de tratamento.*

***Resultados:** Houve aumento significativo no percentual de fios anágenos (34,99%) e redução no percentual de fios telógenos (16,59%) para o grupo tratado, o que não ocorreu no grupo placebo. Houve aumento significativo na cobertura do couro cabeludo das participantes tratadas após quatro meses de uso do produto (33,6%).*

***Conclusões:** O tratamento tópico investigacional foi eficaz na melhora da perda capilar da alopecia androgenética feminina após quatro meses de tratamento.*

***Palavras-chave:** Alopecia; Cabelo; Ensaio clínico; Preparações para cabelo*

Artigo Original

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INTRODUCTION

Androgenic alopecia is among the most common causes of hair loss and among the main complaints by patients in the physician's office. It is characterized by miniaturization of hair follicles and alteration of the hair cycle resulting from action by androgen hormones, with shortening of the anagen phase and lengthening of the telogen phase.[1,2]

Various methods can be employed in the diagnosis of abnormalities in the hair growth cycle, as well as in the evaluation of treatment efficacy. Such methods feature phototrichogram and imaging analysis with macrophotography.[3] Phototrichogram is a non-invasive method in which the hair is cut close on the test region and an image is taken two to three days later for determination of the amount of hairs in the anagen and telogen phases.[2-5]

Macrophotography is used for the capture and comparison of paired images before and after treatment for verification of improvement in hair growth. The analysis requires standardization of the capture conditions and the patient's hair grooming in each moment.[3] The images obtained can be evaluated both visually and by scalp coverage image analysis software.[6]

The current study aimed to investigate the effect of topical treatment with Recrexina® on the improvement of hair loss in female patients with androgenic alopecia, using phototrichogram Dermoscope Dynamic® with Trichoscale® software (FotoFinder Systems GmbH, Bad Birnbach, Germany) and image analysis with macrophotography.

Ethical aspects:

The current study was conducted after ethical approval of the dossier (CAAE: 08929219.1.0000.5386). All participants were oriented on the study protocol and had their questions answered prior to signing the free and informed consent form. All participants gave their consent before being included in the study.

METHODS

Study design

The current clinical trial was prospective, randomized, placebo-controlled, and single-blind.

Participants' inclusion and study site

An invitation was issued to appear at the IPclin Instituto de Pesquisa Clínica Integrada Ltda. (Jundiaí-SP) to 51 female participants presenting androgenic alopecia, ranging in age from 30 to 50 years, with Fitzpatrick skin types I to IV, and who met the inclusion criteria specified in the study protocol.

The inclusion criteria were: age 30 to 50 years; female gender; complaint of hair loss; diagnosis of androgenic alopecia; habit of washing hair at least three times a week; good health status; intact skin on the scalp; Fitzpatrick skin types I to IV; no self-reported risk of becoming pregnant during the study.

The following exclusion criteria were used during the selection process for participants: use of hair appliques; pregnancy or breastfeeding; cicatricial alopecia; immunodeficiencies; active atopic dermatitis; kidney, heart or liver transplant patients; sunburn on the study area resulting from intense solar exposure within a month before the study; use of corticoids, antihistamines, immunosuppressants, retinoids, or anti-inflammatory drugs; other concurrent diseases of the scalp, such as infections, psoriasis, and important seborrheic dermatitis; prior hair transplant or scalp reduction surgery; use of hair extenders or wigs in the last three months; use of minoxidil or finasteride (oral or topical) in the last six months; treatments with low-energy infrared or laser in the last six months; curl softening in the three months prior to the study.

Individuals that consented to participate in the trial underwent the initial dermatologic examination for diagnosis of androgenic alopecia and verification of the inclusion and exclusion criteria, having been divided randomly into two groups (treated versus placebo). They then underwent the phototrichogram examination and had standardized photographs taken with a professional camera (Canon® t3i).

Patient Treatment

After collection of the baseline data, treatment was dispensed to the participants for four months of home use. Patients were instructed to use the investigational product on their clean, dry scalp once a day, massaging it in, from Monday through Friday. Half received the placebo treatment and the other half received the treatment with the study product, according to single-blind randomization.

The investigational product was a topical treatment with human hair follicle stem cells, containing a combination of patented active ingredients, with the brand name Recrexina® Human Follicle Stem Cells - HFSC 100% (Regrowth), (patented by Laboratório Lupin - Medquimica - Juiz de Fora, MG, Brazil).

Phototrichogram analysis

For the phototrichogram analysis, the site was selected on the frontoparietal region for standardized close- cut of hairs on an area of 2cm2. Participants then appeared again two days later for capturing the photographic image of the hairs with the Dermoscope Dynamic® (FotoFinder Systems, Inc., Maryland, USA), using 20X magnification. This procedure was performed before the treatment (baseline visit) and was repeated 120 days after use of the investigational product. In both visits, the analysis was performed in the same region.

At the end, the Trichoscale® software (DermoScan GmbH, Regensburg, Germany) was used to analyze the images with determination of the total number of hairs and the percentage of anagen and telogen hairs. The software performs semiautomatic analysis of the target region.

Analysis of images

Ten participants were selected from the group treated with the investigational product to conduct an evaluation of the efficacy of scalp coverage via macrophotography with subsequent image analysis.

Standardized images were captured from the selected patients before and after the treatment, in the central hair loss region, using a professional camera (Canon® t3i). The captured images were analyzed with the Pro Premier® software (Media Cybernetics, Rockville, USA) to compare the total area of hair loss between the two test times. The analysis was performed as described by Bloch, Escudeiro, and Sarruf (2018).6

Statistical analysis

The treatments were compared between the test times via evaluation of the results obtained with the phototrichogram, using the Student's t-test and processed with SPSS version 22.0. Results of the image analysis (scalp area) were compared between the test times using the paired t-test.

RESULTS

Of the 51 participants included in the trial, 26 were allocated to the treatment arm and 25 to the placebo arm. Of these, 37 concluded the study (20 in the treatment arm and 17 in the placebo arm). The other participants dropped out for personal reasons. Of the 20 participants who concluded the study in the treatment arm, 10 reported mild initial discomfort with use of the product. According to the warnings on the product insert, effects such as redness and temporary heat reaction (generally interpreted by patients as a burning sensation) are expected. Table 1 lists patients' reports of discomfort. According to the phototrichogram analyses, there was a 6.35% mean increase in the total number of hairs between the two test times (before and after treatment) with the investigational product, and a decrease of 6.63% in hairs with the placebo. However, there was no statistically significant difference in the total number of hairs between the two treatments after four months of use.

There was a mean reduction of 16.59% in telogen hairs between the two times with the investigational product, compared to a 23.89% increase in the placebo group, with a statistical difference between the two arms (p-value = 0.010).

The investigational product was associated with a 34.99% increase in anagen hairs after four months, compared to a 29.42% reduction in the placebo group, with a statistically significant difference between the groups for this parameter (p-value = 0.005).

Figure 1 shows the total number of hairs (sum) at each test time according to the study arm. Table 2 summarizes the phototrichogram results. Figures 2 and 3 show the initial and final phototrichogram images of two patients treated with the investigational product.

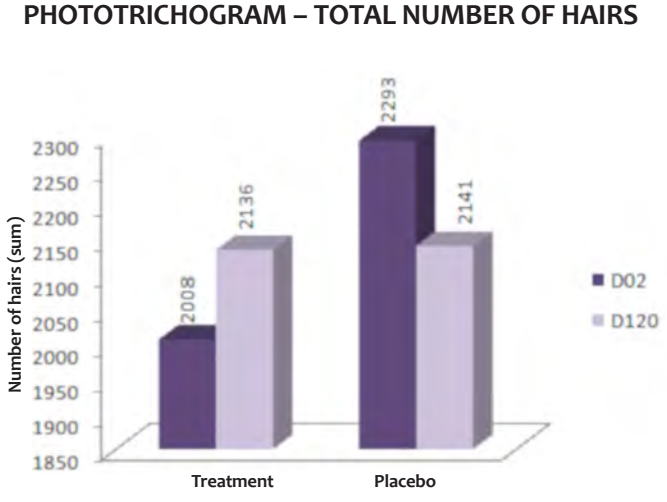
The analysis of macrophotography images used the Image Pro Premier® software to determine the bare scalp area at each test time, based on the method published by Bloch, Escudeiro, and Sarruf (2018)6, for ten participants in the investigational arm.

Figures 4 and 5 show the image analysis of patients treated with the investigational product (before and after). The areas highlighted in red are the bare regions of the scalp. Figure 6 shows the mean bare scalp areas in pixels2 at each test time.

The results show a statistically significant improvement in scalp coverage with four months of the investi-

Table 1: Sensations of discomfort reported by participants after four months of product use (treated group)

Participant's number	Reported sensation
3	Mild burning on posterior scalp with all applications
6	Mild burning right after applications
8	Mild burning right after applications
17	Mild burning after the first application
20	Intense burning on scalp
25	Mild burning after some applications
29	Intense burning with the first three applications
31	When washing hair, the water makes the face red, and burning sensation on ears with all applications
42	When washing hair, the rinse water leaves red streaks on face
51	When washing hair, the rinse water leaves red streaks on face



Key: D02 – analysis before treatment; **D122 –** analysis after treatment.

Figure 1: Total number of hairs before and after treatment according to treatment arm

gational product (p-value = 0.013), with a mean reduction of 33.6% in the bare scalp area. This result proves the efficacy of treatment with the investigational product in promoting new hair growth.

DISCUSSION

We can infer from the results that the investigational product provided significant improvement in the patients' androgenic alopecia, with an increase in the percentage of anagen phase hairs (growth) and a reduction in the percentage of telogen hairs (resting phase) after four months of treatment, compared to the placebo group.

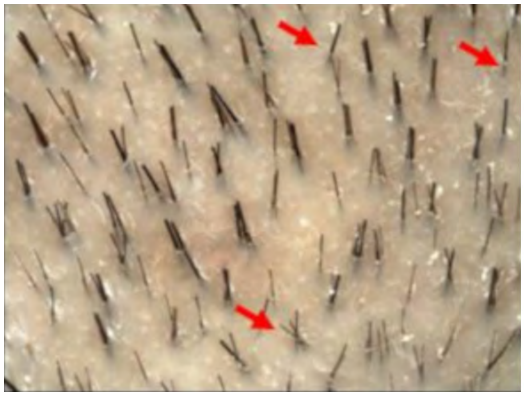
Topical treatment with human hair follicle stem cells has the following mechanisms of action: (1) activation and preservation of bulge stem cells; (2) vasodilatation of the scalp, leading to increased blood flow to the scalp; (3) supply of essential nutrients for hair growth such as amino acids and plant extracts; (4) reduction in activity of the 5α-reductase enzyme (related to balding); and (5) enhancement of capillary keratinization, strengthening the hair.[7]

The investigational product's composition and its mechanism of action corroborate the clinical tests' findings, proving the product's good acceptance and effectiveness for prescription to patients with androgenic alopecia.

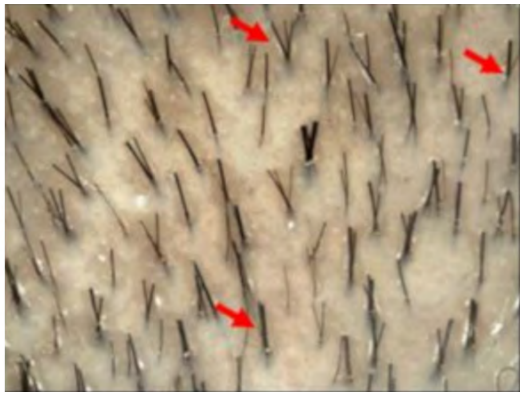
Table 2: Summary of phototrichogram results

Group		Total number of hairs		Telogen hairs		% telogen hairs		Anagen hairs		% anagen hairs	
		Before	After	Before	After	Before	After	Before	After	Before	After
Treated	Mean	100,4	106,8	55,5	46,3	53,3	42,4	44,8	60,5	46,6	57,6
	Sum	2008	2136	1110	926	/	/	896	1210	/	/
	Difference	/	128	/	-184	/	/	/	314	/	/
Placebo	Mean	134,9	125,9	56,1	69,4	41,1	55,0	79,1	55,8	59,1	44,4
	Sum	2293	2141	953	1181	/	/	1344	949	/	/
	Difference	/	-152	/	228	/	/	/	-395	/	/

Key: % = percentage; "before" treatment; "after" four months of treatment

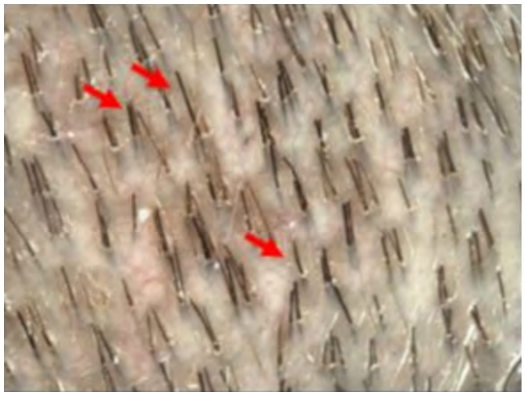


Participant 10 -D02 (Phototrichogram before)

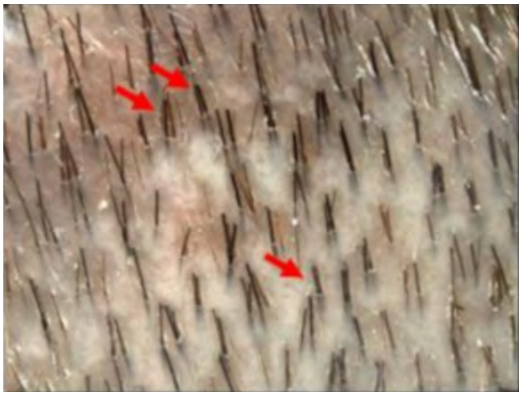


Participante10 -D122 (Phototrichogram after)

Figure 2: Image of phototrichogram analysis before and after in patients in treated group (participant reference number: 10). Arrows indicate increase in quantity of hairs.

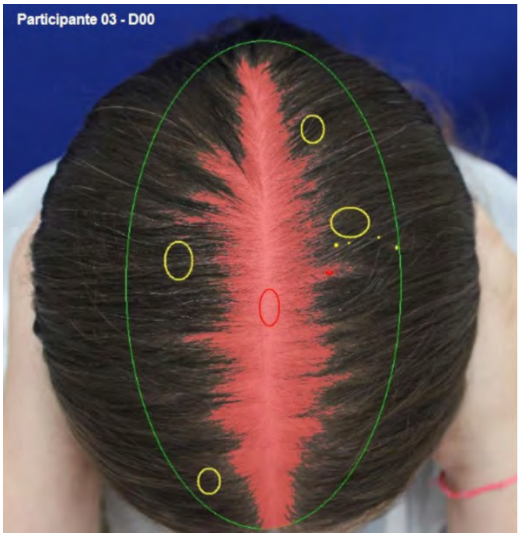


Participant 47 -D02 (Phototrichogram before)

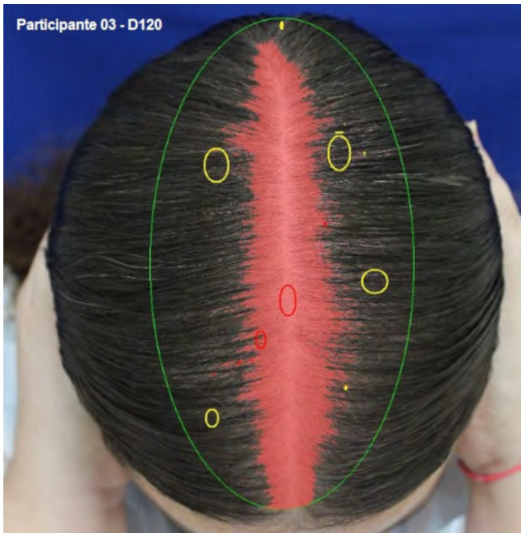


Participant 47 -D122 (Phototrichogram after)

Figure 3: Image of phototrichogram analysis before and after in patients in treated group (participant reference number: 47). Arrows indicate increase in quantity of hairs.

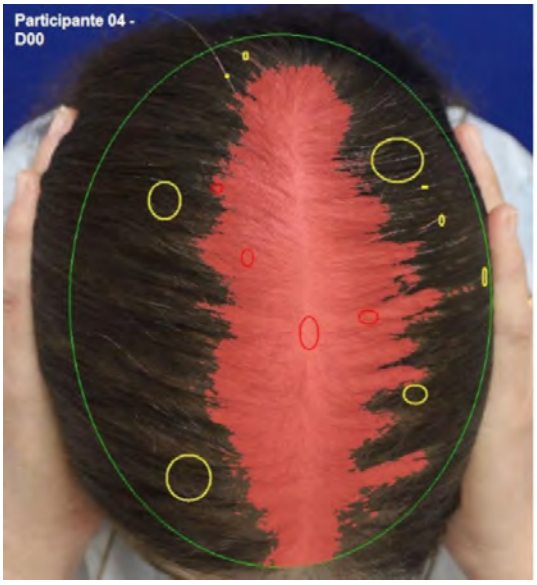


Participant 03 -D00 - analysis before

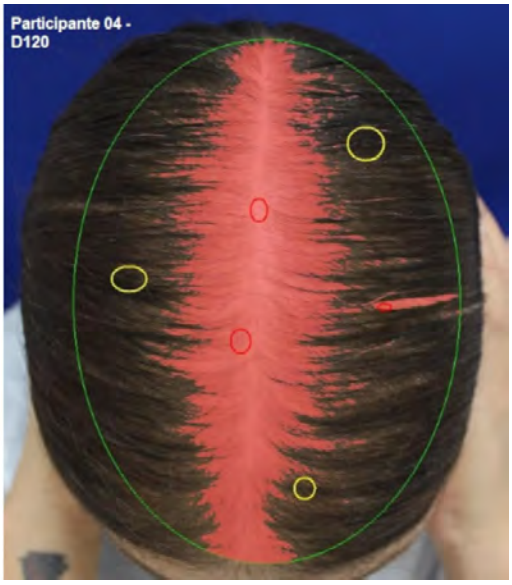


Participant 03 -D120 - analysis after

FIGURE 4: Result of before and after analysis (participant reference number: 03). Participant 03: area on D00 = 121821; area on D120 = 62245; Improvement: 49%

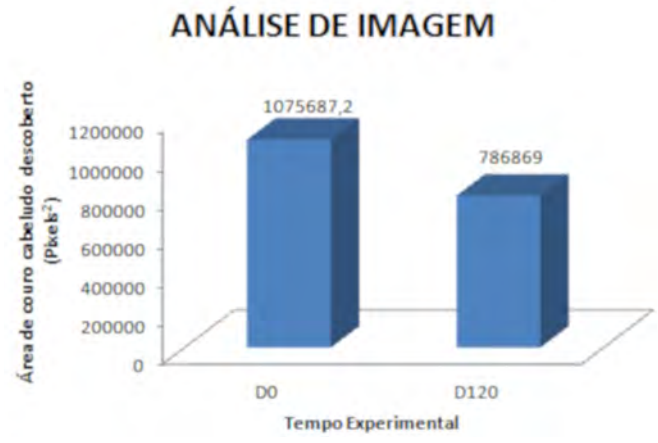


Participant 04 -D00 - analysis before



Participant 04 -D120 - analysis after

FIGURE 5: Result of before and after analysis (participant reference number: 04).
. Participant 04: area on D00 = 813496; area on D120 = 77429; Improvement: 90%



Key: D00 – analysis before; D120 – analysis after

FIGURA 6: Result of before and after image analysis – mean area of uncovered scalp (Pixels2)

CONCLUSION

The product containing human hair follicle stem cells was effective after four months of treatment in patients with androgenic alopecia, when compared to placebo, based on analyses of hair loss with images and phototrichogram, proving to be a treatment with excellent potential.

The investigational treatment led to a 16.59% mean reduction in telogen hairs, a 34.99% mean increase in anagen hairs, and 33.6% mean increase in scalp coverage. ●

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Microneedling in scars treatment: benefits of a single session

Microagulhamento no tratamento de cicatrizes: benefícios de uma única sessão

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ABSTRACT

Introduction: Unaesthetic scars can trigger symptomatic, functional, aesthetic and emotional repercussions. Among the main treatments found today is microneedling.

Objective: Prospective, quantitative study to evaluate the benefits of healing with a single microneedling session.

Methods: A microneedling session was performed on scars of 28 patients. Before performing the procedure with cylinders containing 192 2.5 mm needles and 90 days later, scars are photographed in a standardized manner, having been applied on the Patient and Observer Scar Assessment Scale. Through the performed score, a quantitative evaluation by the analysis of the parameters, being vascularization, pigmentation, thickness, relief, malleability, surface area, pain, itching, color, stiffness, height and irregularity, in addition to the patient's total score and general opinion. and the observer.

Results: All variables obtained improvement, except pain, emphasizing malleability and height. In addition, the overall opinion of the patient and the observer shows 51% improvement. Conclusions: Microneedling is a safe, inexpensive, minimally invasive treatment that delivers experimental results in a single session.

Keywords: Cicatrix; Scales; Therapeutics

RESUMO

Introdução*: As cicatrizes inestéticas podem desencadear repercussões sintomáticas, funcionais, estéticas e emocionais. Entre os principais tratamentos atualmente encontrados está o microagulhamento.*

Objetivo: *Estudo prospectivo, quantitativo, avaliando os benefícios do tratamento de cicatrizes com uma única sessão de microagulhamento.*

Métodos: *Foi realizado uma única sessão de microagulhamento em cicatrizes de 28 pacientes. Antes da realização do procedimento com cilindros contendo 192 agulhas de 2,5mm e 90 dias após, as cicatrizes foram fotografadas de modo padronizado, tendo sido aplicada a Escala de Avaliação Cicatricial do Paciente e Observador. Por meio da pontuação fornecida realizou-se uma avaliação quantitativa através da análise dos parâmetros -sendo eles vascularização, pigmentação, espessura, relêvo, maleabilidade, área de superfície, dor, prurido, cor, rigidez, altura e irregularidade-, além do escore total e opinião geral do paciente e do observador.*

Resultados: *Todas as variáveis obtiveram melhora, exceto a dor, dando destaque à maleabilidade e à altura. Além disso, a opinião geral do paciente e do observador apresentou melhoria de 51%.*

Conclusões: *O microagulhamento é um tratamento seguro, de baixo custo, minimamente invasivo, apresentando resultados eficazes em uma única sessão.*

Palavras-chave: *Cicatriz; Escalas; Terapêutica*

Original Article

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INTRODUCTION

Healing is a dynamic process that requires biochemical and physiological synchrony to have adequate tissue restoration. This mechanism depends on several factors, such as anatomical location, skin type, underlying diseases, age, ethnicity, and the surgical technique used. When the healing involves the dermis completely or extends to the subcutaneous tissue, the lesion becomes noticeable.[1,2]

The most common unsightly scars are hypertrophic, keloid, and atrophic. They can trigger symptomatic, functional, aesthetic, and emotional repercussions. Thus, this condition can cause psychological damage and limit the patient in social and professional relationships. Therefore, the treatment of these lesions is a constant challenge for the physician.[3-5] The patient's eagerness for improvement may be related to the desire to erase unpleasant memories, surprise the partner, or even request a promotion in their work.[6]

The repercussions associated with the emotional condition secondary to the scar include anxiety, social exclusion, depression, interruption of daily activities, sleep disorders, in addition to psychosocial deterioration, with difficulty in reintegrating into the environment in which they lived.[7,8]

Several techniques have been tested to correct post-traumatic skin sequelae. However, many of them are unsatisfactory. Needling methods, such as the subcision, described in 1995, have also been used for the treatment of scars.[9] Currently, one of the proposed treatments is microneedling.

The technique has been improved and increasingly widespread since it is a minimally invasive, simple, inexpensive, safe, and effective procedure. The procedure consists of inducing a controlled lesion on the skin without causing any real damage to the epidermis. The objective is to originate micropunctures that reach the dermis and trigger, with the bleeding, an inflammatory stimulus. Thus, microneedling induces the release of growth factors, which stimulate the formation of new collagen and elastin in the papillary dermis, associating with the production of new capillaries. Then, the association of neovascularization and neocollagenesis after the treatment leads to scar reduction.[10-12] The indications for this procedure are diverse and can be used in rejuvenation as an active vehicle - for example, retinol and vitamin C - or as an isolated stimulus. It also acts on sagging and attenuation of wrinkles. Finally, as already mentioned, it corrects distensible, wavy, and retractable depressed scars, in addition to recent and old stretch marks.[13]

One of the standardized instruments is the disposable cylinder equipped with stainless steel microneedles with length varying from 0.5mm to 3mm and diameter from 0.1mm to 0.25mm. It is essential to highlight the value of the diversity of needle lengths since the intensity of the reaction generated is proportional to this measure. For example, 1.5mm needles promote microchannels that reach the epidermis and dermis, destroying the scar collagen bundles.[14,15] Among the benefits of this procedure, we highlight its good safety profile, which can be applied to all phototypes, including Fitzpatrick skin types IV and V, since it rarely leads to hyperpigmentation. Usually, patients present good tolerability and may have mild erythema and edema, with a quick return to work activities, varying from seven to 10 days, according to some studies. In some cases, there is no need for work leave. Also, it has other advantages, such as collagen stimulation without removing the epidermis; shorter healing time; lower risk of adverse events when compared to ablative techniques; increased skin resistance and thickness; and the possibility of being conducted in sites where there is less concentration of skin annexes.[16,17]

When indicating the procedure, the physicians should pay attention to the contraindications, such as the presence of active acne, oral herpes or any other local infection, psychological disorders that may be exacerbated by the treatment, moderate to severe chronic skin disease (for example, psoriasis), blood dyscrasias, tendency to keloid, use of anticoagulants, treatment with chemotherapy or radiotherapy, and patients who can't understand the technique. Adverse events are not common; however, they can occur. The most frequent are erythema and irritation, which usually disappear within a few hours. There are also reports of post-inflammatory hyperpigmentation, worsening of acne, reactivation of herpes, granulomatous allergic reactions, and local infections when using non-sterile materials.[18,19] In general, most reports state significant improvement, some after just one session. Patients are satisfied with both aesthetic and mobility improvements. Also, they report good tolerability to the procedure, with no complications in most cases. Thus, the effectiveness and safety of this therapy are confirmed.[17,20]

To evaluate the clinical improvement after the treatment is a challenge since there is no single standardized scale for scar assessment. Some of the most used ones are the Vancouver Scale (VSS), Manchester Scar Scale (MSS), Patient and Observer Scar Rating Scale (POSAS), Visual Analogue Scale (VAS), and Stony Brook Scar Evaluation Scale (SBSES), based on subjective parameters, but used objectively. Among these, POSAS stands out, as it considers the assessment of both the physician and the patient, elucidating the characteristic of the lesion reliably.[21,22]

The present study aimed to quantify the clinical improvement of surgical scars, including post-traumatic scars and breast prosthesis, cesarean section, or skin biopsy, after a microneedling session, assessing the results using POSAS.

METHODS

This study was conducted at the Dermatology Outpatient Clinic of the Universidade Federal do Triângulo Mineiro (UFTM), after the approval by the institution's Research Ethics Committee.

Thirty patients were randomly selected, who had a link to the Outpatient Clinic of the Hospital de Clínicas da UFTM with unsightly and/or dysfunctional scars resulting from aesthetic procedures, such as breast prosthesis, car accident trauma, stab wounds, cesarean section, cholecystectomy, or skin biopsy. Exclusion criteria were: less than 18 years old; cognitive deficit; presence of any active lesion at the procedure site; moderate to severe chronic skin diseases, such as eczema or psoriasis; blood dyscrasias; tendency to keloid; use of anticoagulants; treatment with chemotherapy or radiation therapy.

After selection, the patient was instructed on the risks and benefits of the procedure. Then, the scar was photographed, and the Patient and Observer Scar Assessment Scale (POSAS) was applied. The procedure was performed in an exclusive operating room of the Dermatology Service of the UFTM Specialty Outpatient Clinic, having been performed by resident dermatologists assisted by the dermatologist responsible for the Service. After antisepsis with chlorhexidine 2%, anesthesia was performed with lidocaine solution 2% without vasoconstrictor, diluted 1:4 with 0.9% saline solution, and injected into the skin with a 31G needle. The intervention was followed using of a cylinder studded with stainless steel microneedles, totaling 192 units with 2.5 mm length (Dr. Roller®, Moohan Enterprise CO., Gyeonggido, South Korea), with back and forth movements guided by a uniform pattern of petechiae throughout the treated area, reaching a deep injury. According to some studies, 10 to 15 passes must be made in the same direction, and at least four crossing passes in the rolling areas. At the end of the procedure, a gauze dressing was applied over the lesion, and the patient was instructed to remove it after 24 hours with running water, and initiate then the use of a dexpanthenol-based skin regenerator for 10 days. Also, the importance of photoprotection was stressed. All patients received the same treatment protocol and guidelines. After 90 days of the procedure, the questionnaire was applied again, and the lesion was photographed. It is worth mentioning that the data and photos taken in the first evaluation were not made available to the observer and the patient.

The variables analyzed at POSAS by the observer were: vascularization, pigmentation, thickness, texture, malleability, surface area, and general opinion; and those of the patient were pain, itching, color, stiffness, height, irregularity, and general opinion. The score ranged from 1 to 10, with the minimum value being normal skin and 10 the worst scar imaginable. For assessment of the results, the Wilcoxon test 23 was applied to compare day 0 to day 90.

RESULTS

Thirty patients were selected and, since the sample proportion is unknown, the sample was calculated from a 90% confidence level and a maximum error of the estimate of 15%.[24-25] However, two were lost to follow-up. All those who completed the study reported bearable pain during the procedure. Also, the return to work activities ranged from three to five days, according to the extent of the injury. Of the 28 patients assessed, four had no desire to repeat the procedure, due to complete improvement, and the others wished to perform it again. There were no complications, such as hypertrophic scarring or infections. The patients' skin phototypes varied from II to IV, according to the Fitzpatrick scale.

The comparative analysis between D0 and D90 of the vascularization, pigmentation, thickness, texture, malleability, surface area, pain, itching, color, stiffness, height, irregularity, general opinion of the patient and the observer was performed using the Wilcoxon test.[23] Table 1 shows the results.

After the experiment and the hypothesis test, it is noted that the vast majority of parameters are changed when comparing the skin on the day of application and after 90 days of use (p-level <0.05). All parameters of the observer rejected the null hypothesis, that is, vascularization, pigmentation, thickness, texture, malleability, and surface area, presenting differences when comparing the start and the end date. When assessing the patient's scale, the pain parameter does not reject the null hypothesis, that is, it did not change from one period to the next, while itching, color, stiffness, height, and irregularity varied.

We calculated the averages of each of the parameters for comparison. Except for pain, which had no difference between the averages in the two periods, we observed that the other parameters showed a reduction in the average scores. This represents an improvement, since the lower the value for the scale, the closer it is to the characteristics of normal skin. Tables 2 and 3 show the results. Malleability and height were the parameters that obtained the highest average reductions in percentages between the scores in the two periods, while vascularization and stiffness obtained the smallest reductions for the observer and patient scale, respectively. Even so, those with the smallest changes showed considerable average reductions (a minimum of 40%).

Considering the frequencies of the patient's scale parameters, the pain parameter was the only one that showed a different behavior from the rest. When analyzing the other parameters of the patient's scale, we can observe a similar behavior to that of the observer's score since they concentrated on the lower levels of the scale after 90 days.

Furthermore, to the assessment of the parameters, the general opinions of both the observer and the patient were studied. The hypothesis tests rejected the null hypothesis ($p<0.05$), indicating a change in the opinion of those involved from one period to the next. The changes in the general views of the observer and the patient were positive since the average grades of these parameters were reduced by 51%, representing greater proximity to normal skin after 90 days.

In terms of frequency distribution, we can visualize the opinion change of those involved in the study. The frequencies of the general views of the observer and the patient were analyzed. We can observe that, in both distributions, the concentration shifted from the right to the left side of the graph, showing the change in the grades from one period to the next. The patient's opinion, for example, had a higher incidence (39%) in grade 10 in the initial period. On day 90, the highest incidence (32%) was for grade 1.

DISCUSSION

This study selected 30 patients; however, two were lost to follow-up. Among the 28 subjects who completed the treatment, four patients revealed that they would not like to undergo the procedure again, as they were already satisfied with the result. However, the others wanted new sessions, despite the initial satisfactory result. According to a study conducted in 2017, despite the different results, all patients showed satisfaction and interest in following the treatment after microneedling.[26]

All patients reported good tolerability to the procedure, as expected by the authors. Also, there were no reports of adverse events or complications, proving to be a safe and mi-

nimally invasive technique. As already described, as the epidermis is maintained, microneedling has a low risk of infection and post-inflammatory hyperpigmentation. Another advantage of this treatment is the short recovery time. In the present study, patients returned to work activities in two to four days.[27-29]

Through the application of POSAS, we could quantitatively assess the following variables, according to the observer: vascularization, pigmentation, thickness, texture, malleability, surface area, and general opinion. The patient's variables were: pain, itching, color, stiffness, height, irregularity, and general opinion. The score ranged from 1 to 10, with the minimum value being normal skin and 10 the worst scar imaginable. The pain criterion did not vary between the first and the second questionnaire; however, all patients scored 1 in this regard, that is, equal to normal skin from the beginning.

Among the evaluated criteria, except for pain, we noticed an improvement in all aspects, highlighting malleability and height (Figures 1 and 2). Published studies show that microneedling promotes the degradation of dense collagen in the misaligned fibers of the healing process, allowing the realignment of collagen fibers and promoting the minimization of irregularities, reduction of scar volume, increased sensitivity, and elastin synthesis. Consequently, there is an improvement in the scar distensibility, reducing hyperpigmentation and normalizing the keratinocyte-melanocyte relationship.[29]

In the present study, one of the patients had a scar on the face with mobility difficulties, requiring physiotherapy. After the procedure, the physical therapist noticed an improvement in the condition during the movements. Microneedling can improve flexibility and elasticity, as shown by other studies.[30-32]

In 2018, a study used POSAS to assess the improvement of scars after microneedling, and the results pointed to an increase in scar quality with a significant tendency to normal skin. The general opinion showed a 51% improvement for both the patient and the observer, corresponding to the values found in this study.[33] Microneedling stimulates the synthesis of significant structural and skin reconstruction elements (collagen, elastin, proteoglycan), being used in the treatment of many skin defects, with high effectiveness in cases of scarring.[34] Therefore, it was chosen as the only form of therapy in this study.

One of the objectives of this study was to assess clinical improvement with just one session. However, partial improvement implies the need to prolong treatment. A study conducted in 2014 on rats to investigate the effects of repetitive treatments showed the best results when the treatment was repeated four times with an interval of three weeks. Therefore, with the largest number of sessions, better results can be obtained.[31] It is noteworthy that the patient's opinion, the prospects for improvement and the true degree of dissatisfaction are essential for conducting any procedure or deciding to prolong the therapy.[6]

CONCLUSION

Microneedling is a safe, low-cost, effective, and minimally invasive treatment. With just one session, satisfactory results can be obtained, but others may be necessary. The method includes the improvement of several relevant aspects in the analysis of scars, such as malleability and height. In addition to the aesthetic improvement, the functional enhancement of the affected site should be highlighted. Therefore, considering the good tolerability and the high degree of patient and observer satisfaction, this procedure is an excellent therapeutic option for scarring.

Therefore, knowing its technique and indications is essential for training young dermatologists. ●

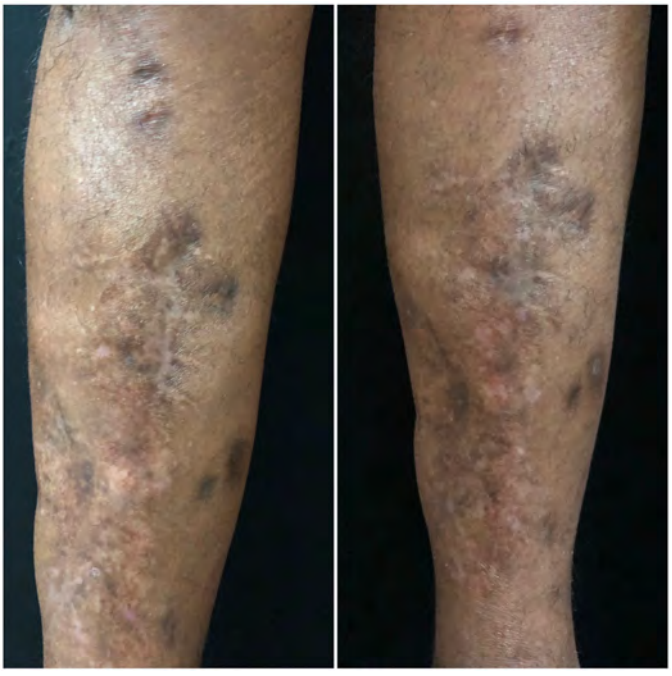

Figure 1: First photo: before the procedure. Second photo: 90 days after the procedure

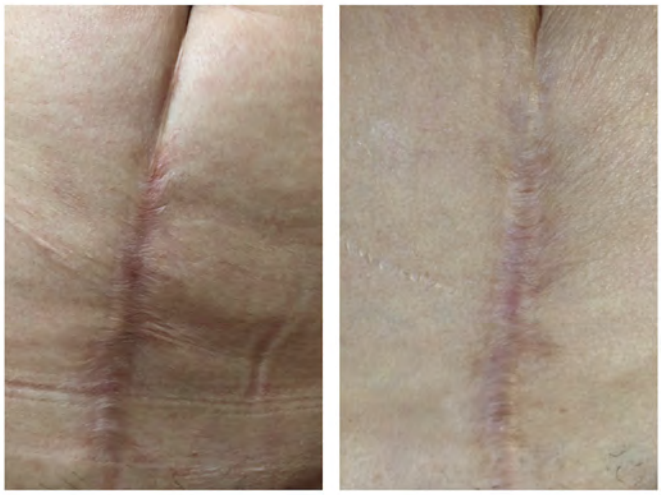

Figure 2: First photo: before the procedure. Second photo: 90 days after the procedure

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Data collection, analysis, and interpretation.

Shave biopsy for differential diagnosis of lentigo maligna on the face and scalp: diagnostic approach

Biópsia por saucerização para diagnóstico diferencial de lentigo maligno na face e no couro cabeludo: abordagem diagnóstica

Original Article

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ABSTRACT

Introduction: Lentigo maligna is a subtype of melanoma in situ, which affects sun-exposed areas. On the face, it can have a clinical and dermoscopic appearance similar to several benign pigmented lesions. Differential diagnosis between them is fundamental for the appropriate therapeutic and should be made by histopathological analysis. Excisional biopsy is the gold standard, but in large, unresectable lesions or in difficult anatomical sites, it can have aesthetic or functional implications. In these cases, shave biopsy appears to be a safe and reliable alternative.
Objective: To describe an appropriate shave biopsy technique, discuss its results and indications in the outpatient routine of the dermatologist.
Methods: Sixteen patients with suspected : Lentigo maligna on the face and scalp were selected. Inclusion criteria were older than 18 years, lack of diagnosis and previous treatment, flat lesions larger than 8 mm and suggestive clinical and dermatoscopic signs. The approach performed was shave biopsy.
Results: The diagnosis of : Lentigo maligna was confirmed in 25% of the cases, and a widening of margins presented compatible results in 100% of them.
Conclusions: Shave biopsy seems to be a suitable alternative for flat lesions without clinical and dermoscopic criteria of vertical growth.
Keywords: Acne Vulgaris; Diclofenac; Inflammation; Hyperpigmentation

RESUMO

Introdução*: O lentigo maligno é um subtipo de melanoma in situ que acomete áreas de intenso dano solar. Na face, ele pode ter aspecto clínico e dermatoscópico semelhante a diversas lesões pigmentadas benignas. O diagnóstico diferencial entre elas é fundamental para abordagem terapêutica adequada e deve, preferencialmente, ser feito pela análise histopatológica. A biópsia excisional é o padrão ouro, porém em lesões grandes, irressecáveis ou em locais de difícil abordagem ela pode gerar grande prejuízo estético e funcional. Nesses casos, a biópsia por saucerização parece ser uma alternativa segura e fidedigna.*
Objetivo: *Descrever a técnica adequada da saucerização, discutir seus resultados e suas indicações na rotina ambulatorial do dermatologista.*
Métodos: *Foram selecionados 16 pacientes com suspeita de lentigo maligno na face e no couro cabeludo. Os critérios de inclusão foram idade maior que 18 anos, ausência de diagnóstico e tratamentos prévios, lesões planas, maiores que 8mm e com sinais clínicos e dermatoscópicos sugestivos. A abordagem realizada foi biópsia por saucerização.*
Resultados: *O diagnóstico de lentigo maligno foi confirmado em 25% dos casos, e a ampliação de margens apresentou resultado compatível em 100% deles.*
Conclusões: *A biópsia por saucerização parece ser uma alternativa adequada para lesões planas sem evidências clínicas e dermatoscópicas de crescimento vertical.*
Palavras-chave: *Biópsia; Diagnóstico; Lentigo; Melanoma; Procedimentos cirúrgicos ambulatórios*

INTRODUCTION

The term "melanoma in situ" was first used in 1949 by Lever, but it was only in 1992 that this classification was officially recognized as a diagnostic category for melanomas.[1] In melanoma in situ, neoplastic cells are confined to the epidermis and the adnexal epithelium, not exceeding the basal layer of these structures.[2]

Among the melanomas in situ, lentigo maligna (LM) affects areas of intense sun damage, preferably head and neck, with a peak incidence between 65 and 80 years of age.[2] It represents one of the clinical and pathological forms of melanomas in situ and may have a prolonged evolution, up to several decades, before evolving to its invasive form, lentigo maligna melanoma (LMM).[3]

Lentigo maligna presents, from the clinical point of view, as a macule with irregular, poorly-defined edges, varied pigmentation with asymmetrical distribution, and slow growth.[3] Its appearance can be very similar to other pigmented lesions of the face, whether benign, such as seborrheic keratoses and solar lentigo; pre-malignant, such as actinic keratoses; and malignant, such as pigmented basal cell carcinoma. The differentiation between these entities is of great importance for the planning of the therapeutic approach.

Dermoscopy is a non-invasive complementary exam that helps in the differential diagnosis between these lesions. Dermoscopic criteria indicative of LM are rhomboidal structures, irregular pseudonetwork with asymmetrical follicular openings, slate-gray granularity, and blots.[3]

However, in most cases, the definitive diagnosis of pigmented lesions depends on histopathological analysis. The ideal biopsy technique should be easy and quick (to facilitate generalized application), be associated with minimal morbidity, allow precise staging of lesions considered to be malignant, and do not compromise oncological results in the long term.4 Excisional biopsy is regarded as the gold standard for the possibility of extensively assessing the removed tissue and accurately defining cell atypia and the presence or absence of basement membrane invasion, Breslow index, and other prognostic factors involved in melanocytic neoplasms. However, there are some cases in which it can cause a significant aesthetic and functional damage, as in large, unresectable pigmented lesions and in places that are difficult to approach, such as the face. In these cases, incisional biopsy guided by dermoscopy has been considered as the recommended initial approach.

The incisional punch biopsy is widely used, and its main advantages are its ease of execution and the potential to provide accurate information on the T stage, as it usually extends to subcutaneous fat and encompasses the base of the primary tumor. However, it is generally performed with small punch sizes, 3 mm or 4 mm, and the largest tools available for its performance measure 6 mm to 8 mm. In larger lesions, it may not cover the entire periphery of the injury. Thus, it can lead to diagnostic errors by preventing the analysis of essential criteria such as symmetry, overall size, and circumscription of the tumor, or even underestimating the actual invasion of the tumor by sample error if it does not include the deeper portion of the lesion.4

Incisional biopsy by shaving, or shave biopsy, which is the target of our study, seems to be superior to punch biopsy in the initial evaluation of superficial and extensive pigmented lesions.[5] This type of technique is quick and practical and can be performed in the dermatologist's office under local anesthesia, allowing a higher tissue sampling without compromising functionally or aesthetically.

This study aims to describe the proper shave biopsy technique, discuss its results and indications for the initial approach on pigmented lesions on the face in the outpatient routine of the dermatologist.

METHODS

This is a pilot study. Sixteen patients were selected at the Dermatology outpatient clinics of the Santa Casa de Misericórdia in Porto Alegre between May and October 2019 with suspected lentigo maligna on the face and scalp. The lesions were previously assessed by dermoscopy, and the criteria used for the selection included patients aged over 18 years old, without previous diagnosis and treatment, with the presence of flat pigmented lesions, larger than 8 mm, and with dermoscopic signs suggestive of LM.

The biopsy technique used was deep shaving or shave biopsy, as shown below (Figure 1). The technique consists of asepsis, infiltration of local anesthetic, application of a thin layer of ointment on the lesion to firm the tissue (due to the availability in our service, we used mupirocin), followed by the removal of a disc of tissue using a scalpel or curved razor blade. It produced a sample extending to the upper dermis or the mid-dermis, depending on the angle of the blade. Hemostasis was performed with the application of aluminum chloride and a compressive dressing for 24 hours.

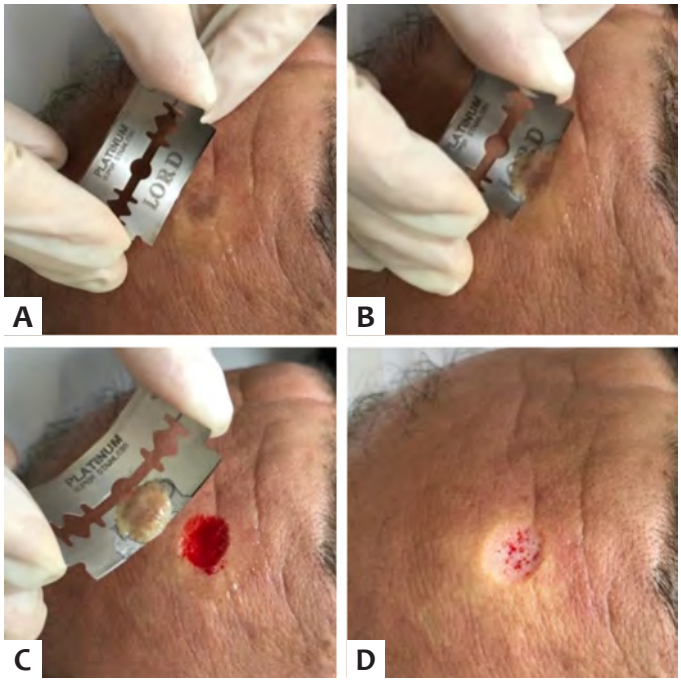

FIGURE 1: A - After applying a thin layer of ointment; **B and C**- Removing the disc of tissue; D - Immediate after.

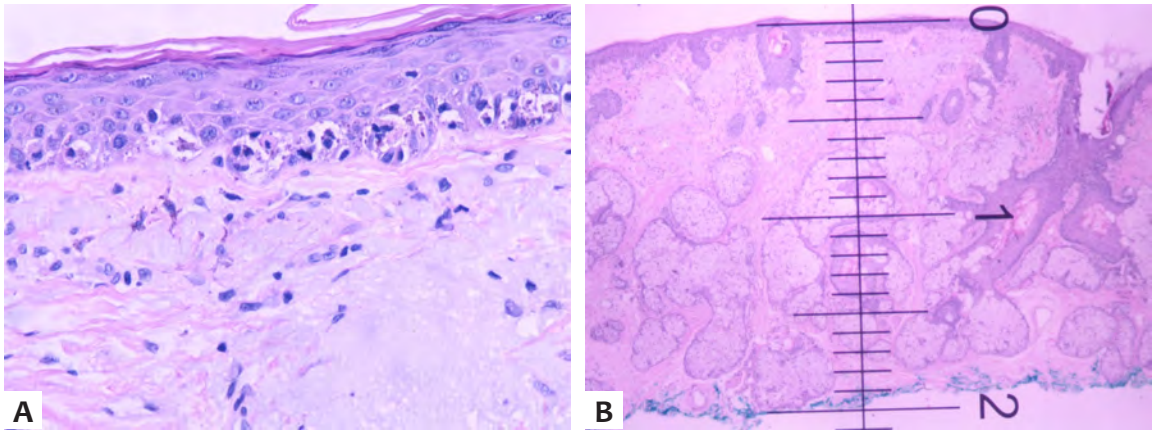

Figure 2: A Lentiginous proliferation of the basal layer (HE, x5); **B -** Shaving thickness (HE, x5)

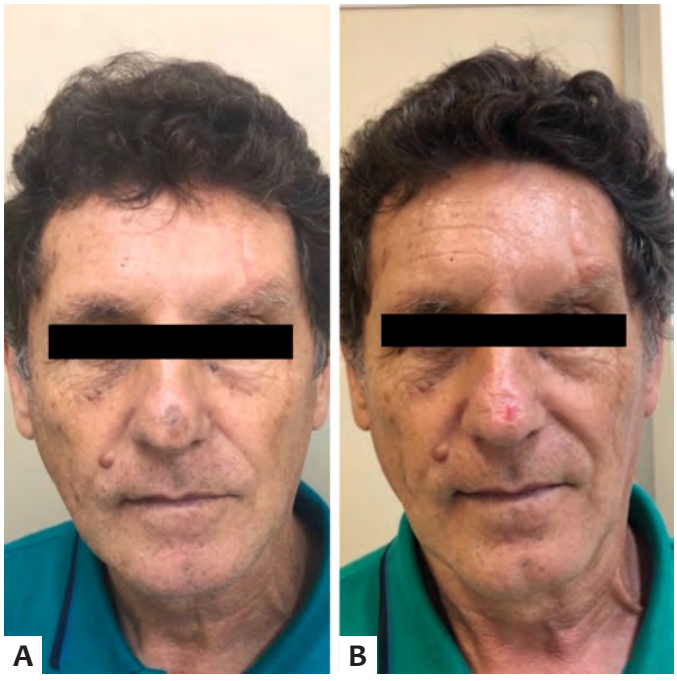

Figure 3: A - Preoperative; **B -** 30 days after the shave biopsy. Confirmed case of lentigo maligna with free margins after the shave biopsy

Table 1: Sample characteristics (n=16)

	N	%
Age	68,7 +- 12,2	
Sex		
F	8	50
M	8	50
Site		
Nasal	5	31
Front/ eyebrow	3	19
Malar/Mandibular	6	38
Scalp	2	13
Results		
Actinic keratosis	6	38
Seborrheic keratosis	2	13
Lentigo simplex	3	19
Lentigo maligna	4	25
Melanose actínica	1	6
Ampliação de margens	3	19
Lentigo maligno	2	67
Ausência de neoplasia	1	33

RESULTS

Our study selected 16 patients aged 36 to 87 years, with flat-pigmented lesions on the face and scalp suggestive of lentigo maligna. All of them underwent the shave biopsy. Table 1 summarizes the results.

The diagnosis of lentigo maligna was confirmed in 4 patients. Of these, 3 underwent margin enlargement, and post-enlargement histopathology was compatible with the initial diagnosis in all cases. The fourth patient is undergoing clinical follow-up, as he presented deep and peripheral margins free of lesion already in the initial approach. Figure 2 represents the histopathological diagnosis, and Figure 3 illustrates the postoperative evolution, with a satisfactory aesthetic result.

DISCUSSION

The analysis of the data suggests that the shave biopsy appears to be a safe and reliable alternative in the initial approach of flat-pigmented lesions with suspected melanoma in situ. Histopathological analysis after margin enlargement confirmed the initial diagnosis or didn't find residual neoplasia in 100% of the cases, a fundamental data for the safety of using the technique since one of the main concerns of this type of approach is the underestimation of the Breslow index by transection of the tumor base.[6]

These results are in line with those was seen by Pariser et al.[7] in their study, which assessed the quality of the materials collected by excisional, punch, deep, and superficial shaving biopsies, with considerable superiority of the material obtained by deep shave biopsy in comparison to punch and superficial shave biopsies, and certainty of histological diagnosis similar to cases submitted to excision.5

Also, the results of our study confirmed that several benign pigmented lesions are part of the differential diagnosis of

melanoma, and reinforce the relevance of more conservative initial approaches in prime areas to reduce functional and/or aesthetic sequelae.

CONCLUSION

Excisional biopsy with narrow margins is the most appropriate initial approach for pigmented lesions suspected of lentigo maligna. Although, it is not practical for most cases of extensive injuries since it requires more time and cost to be performed, in addition to technical difficulties for professionals without experience in advanced dermatological surgery. Incisional biopsies are routinely performed on large pigmented lesions, located in prime areas or by professionals who are not specialized in surgery, or who do not have a favorable environment for the appropriate excision of the lesion. Shave biopsy appears to be an adequate technical alternative for flat lesions without evidence of vertical growth. In addition to being performed quickly and having excellent aesthetic results, it presents an adequate tissue sample, diagnostic accuracy, and the possibility of safety assessment of the deep margins of flat lesions. ●

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Characteristics of sunscreen application on the face of Brazilian skin cancer patients

Características da aplicação de filtro solar na face por brasileiros previamente diagnosticados com câncer da pele

Communication

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ABSTRACT

Introduction: Photoprotection is indicated to reduce the exposure to cutaneous actinic damage and it is important to prevent skin cancer. The face is the most irradiated area of the body and is also where skin cancers most commonly occur.

Objective: To evaluate the amount of sunscreen applied and its facial coverage in patients previously diagnosed with skin cancer, treated at a Brazilian public institution.

Methods: Quasi-experimental study involving 40 patients undergoing skin cancer follow-up. Participants were asked to apply sunscreen on their face, as usual, and the mass used was measured. After, participants were photographed under Wood's light to evaluate the homogeneity of the sunscreen´s coverage, and facial sunscreen coverage failure.

Results: Fourteen (35%) participants applied an estimated amount lower than recommended (2mg/cm2). The regions with smallest coverage were the ears and the "H" area of the face.

Conclusions: The insufficient or heterogeneous sunscreen application on face, neck and ears may promote a false perception of protection, leading to irresponsible exposure. As the population ages and the incidence of skin cancers increases, it is essential to stimulate photoprotection, with appropriate information, especially among high-risk individuals.

Keywords: Sunscreening Agents; Skin Neoplasms; Sunburn; Sunlight

RESUMO

Introdução: *Fotoproteção é indicada para reduzir a exposição ao dano actínico cutâneo, sendo relevante para a prevenção ao câncer da pele. A face é a área mais irradiada do corpo e é o local mais comum de ocorrência de tumores.*

Objetivo: *Avaliar a quantidade aplicada de fotoprotetor tópico e a cobertura facial obtida por pacientes em seguimento por câncer da pele em uma instituição pública brasileira.*

Métodos: *Estudo quasi-experimental envolvendo 40 pacientes oncológicos cutâneos. Foi solicitado que aplicassem filtro solar em suas faces (da forma como faziam habitualmente), e a quantidade (massa) utilizada foi aferida. Após, os participantes foram fotografados sob a luz de Wood para avaliar a homogeneidade da cobertura e as áreas faciais nas quais a cobertura falhou.*

Resultados: *Quatorze participantes (35%) aplicaram uma quantidade menor do que a recomendada (2mg/cm2). As regiões com as menores coberturas foram as orelhas e a zona "H" da face.*

Conclusões: *A aplicação insuficiente ou heterogênea de filtro solar em face, pescoço e orelhas promove falsa percepção de proteção, podendo acarretar uma exposição irresponsável. Conforme a idade da população e a incidência do câncer da pele aumentam, é essencial estimular a fotoproteção, por meio de informações apropriadas, especialmente entre indivíduos de alto risco.*

Palavras-Chave: *Protetores solares; Neoplasias cutâneas; Queimadura solar; Luz solar*

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INTRODUCTION

Photoprotection is indicated for reducing exposure to actinic damage to the skin and is highly relevant for the prevention of skin cancer.[1] Despite the lack of strong evidence on the effectiveness of sunscreen use in the prevention of melanoma and basal cell carcinoma, sunscreens are prescribed for all skin cancer patients.[2,3]

The face is the area of the body that receives the most sunlight and is also the most common site for the occurrence of skin cancer.[4] No study to date has assessed the quantity and quality of sunscreen use on the face by Brazilians previously diagnosed and treated for skin cancer.

This study aimed to assess the amount of topical sunscreen applied and the facial coverage obtained by patients previously diagnosed with skin cancer and treated in a Brazilian public institution.

METHODS

This was a quasi-experimental study with 40 patients in follow-up at the Dermatology Outpatient Clinic of the University Hospital, Botucatu School of Medicine, in São Paulo State, Brazil, and who had been treated previously for skin cancer. Participants were included consecutively by convenience, following their dermatology appointments. The research project was approved by the hospital's Institutional Review Board.

Participants were asked to apply sunscreen (Anthelios Airlicium SPF 60, La Roche Posay) on their faces as they normally did at home. Without the patient's knowledge, the tube containing the product had been weighed in advance.

The face has an estimated surface area of 300 to 350 cm^2 (data not shown), which would require 600 to 700mg of sunscreen to guarantee the recommended density of 2mg/cm^2.5 The facial area was estimated with paper face molds of ten individuals of both sexes and median height. Following the sunscreen application, participants were photographed under Wood's light to assess the homogeneity of sunscreen coverage. Facial areas with gaps in the coverage (<10% of the anatomical area) were recorded for each participant and displayed in a heat diagram.

RESULTS

Of the 40 participants, men represented 67% of the sample, and mean age (standard deviation) was 75 (9) years. Mean (standard deviation) amount of sunscreen applied to the face was 1 (0,6) gram, and 14 participants (35%) applied less sunscreen than recommended (2mg/cm2), with no difference between men and women (p=0.42). There was an inverse correlation between participants' age and the amount of sunscreen applied (r= –0.51; p<0.01).

Table 1 and Figure 1 show information on uniformity of application. The areas with the lowest coverage were the ears and "H" zone of the face (nasolabial, nasal, periocular, and auricular regions).[6]

Table 1: Coverage of face areas and ears, assessed with Wood's light (n = 40)

Topography	N (%)
Malar	35 (88)
Chin	31 (78)
Temples	30 (75)
Mid-Forehead	30 (75)
Eyebrows	27 (68)
Nasal wings	26 (65)
Hairline	25 (63)
Nasal tip	24 (60)
Lower lip	17 (43)
Glabella	15 (38)
Upper lip	15 (38)
Upper eyelids	14 (35)
Lower eyelids	14 (35)
Medial epicanthus	7 (18)
Ears	2 (5)

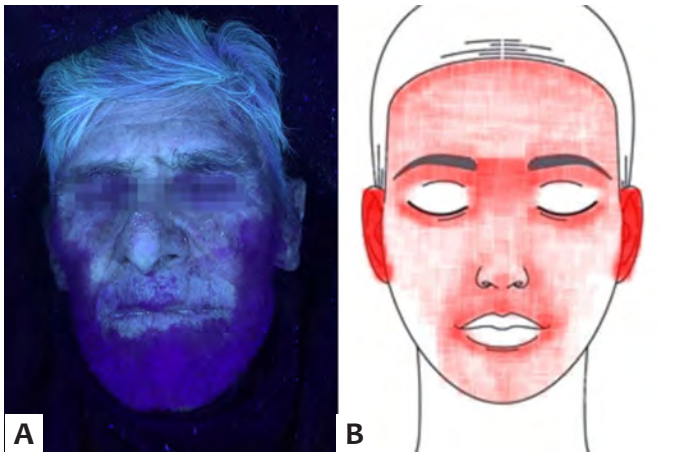

Figure 1: Representation of facial coverage with sunscreen under Wood's light. **(A)** Example of heterogeneous sunscreen application, neglecting upper lip, nasal region, and forehead. **(B)** Heat diagram of regions of the face with less sunscreen coverage, where dark red areas indicate less coverage (n = 40)

DISCUSSION

An excessively thin layer of sunscreen fails to properly block sunrays. A reduction of 50% in the amount of SPF 30 topical sunscreen leads to a 63% reduction in its effective SPF (sun protection factor).[7]

In the current study, besides the inadequate amount of sunscreen that they applied, patients who had already been diagnosed and treated for skin cancer showed gaps in coverage of the face, especially on regions where neoplasms behave more aggressively, such as the ears and periocular and perinasal regions. An Australian study also identified inadequate application of sunscreen as one of the causes of unintentional sunburn, a known risk factor for skin cancer.[8] Besides, elderly individuals may present impaired sight and motor coordination, which can affect adequate sunscreen application.

The current study's limitations include the fact that it was conducted in a single center and only evaluated elderly patients.

In addition, the study only evaluated patients in follow-up at a public dermatology service and did not systematically evaluate sunscreen application on the face.

CONCLUSIONS

The promotion of photoprotection in skin cancer patients should include educational measures such as safe solar exposure time, mechanical protection (long clothing and hats), and adequate use of topical sunscreen (which however should not be an excuse for increasing solar exposure time). Insufficient or uneven sunscreen application on the face, ears, and neck gives the false impression of protection and can lead to careless solar exposure, especially in patients at increased risk of developing skin cancer.

As the population ages and skin cancer incidence increases, it is essential to encourage photoprotection through appropriate information, especially in individuals at high risk. ●

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Angiokeratoma circumscriptum: clinical features, dermoscopy and surgical approach

Angioqueratoma circunscrito: clínica, dermatoscopia e tratamento cirúrgico

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ABSTRACT

Angiokeratomas are vascular malformations constituted by telangiectasia of preexisting vessels. They are not classified as angiomas. It is the rarest variant of angiokeratomas, with few cases in the literature. The mechanism of development of these lesions has not yet been fully elucidated. Small lesions can be treated with electrosurgery, curettage, or cryosurgery. Larger lesions require deep surgical excision, and depending on the size and depht of the lesion, direct closure, flap, or grafting. CO2 or argon laser are considered other treatment options. In this case report we describe a classic case of circumscribed angiokeratoma, with onset at birth, and progressive growth.

Keywords: *Ambulatory surgical procedures; Dermatology; Vascular malformations*

RESUMO

Angioqueratomas são malformações vasculares constituídas por telangiectasias de vasos preexistentes, não sendo considerados angiomas propriamente ditos. O tipo circunscrito é o mais raro dos angioqueratomas, com poucos casos descritos na literatura mundial. O mecanismo de desenvolvimento destas lesões ainda não foi completamente elucidado. Lesões pequenas podem ser tratadas por eletrocauterização, curetagem ou criocirurgia. Lesões maiores requerem excisão cirúrgica profunda e, dependendo do tamanho do defeito, fechamento direto, retalho ou enxerto. Outras opções incluem laser de CO2 ou de argônio. Neste relato de caso descrevemos um quadro clássico de angioqueratoma circunscrito, com aparecimento ao nascimento e crescimento progressivo até a idade adulta.

Palavras-Chave: Dermatologia; Malformações vasculares; Procedimentos cirúrgicos ambulatórios

INTRODUCTION

Angiokeratomas are relatively rare vascular malformations characterized by asymptomatic skin lesions. They are telangiectasias of pre-existing vessels and are not considered angiomas.[1] The capillaries in the papillary dermis dilate, with secondary epidermal changes, with hyperkeratosis and acanthosis.[2] Angiokeratoma circumscriptum is the rarest variant of angiokeratomas.[3]

Clinically, angiokeratomas appear as multiple hyperkeratotic dark red to black, papule, and plaques. Sometimes they are friable, with minimal trauma bleeding. They vary in size, depth, and location.[4] Most commonly, they occur in the lower limbs, in segmental distribution.

In most cases, the lesion is already noticed at birth, but it rarely develops late in childhood or adolescence. There are no reports of spontaneous regression.[4]

Other clinical forms of angiokeratomas include 1. Angiokeratoma corporis diffusum (Fabry's angiokeratoma); 2. Mibelli's angiokeratoma (occurs on the back of the phalanges of hands and feet de); 3. Angiokeratoma of Fordyce's (scrotal region); 4. Solitary papular angiokeratoma (the most common form).[1-5] There is also the circumscribed neviform angiokeratoma, which is an even rarer variant of the angiokeratoma circumscriptum.

The exact mechanism of development of these lesions has not yet been fully elucidated.[5]

CASE REPORT

A 25-year-old man reported lesions on the left lower limb since birth. Initially, they were dark red lesions, with little elevations, segmental, on the lateral aspect of the left leg. Over the years, the injury changed, becoming hyperkeratotic, elevated, and bleeding (Figure 1). The patient sought our Service due to the friability and pain in the elevated lesions, which bothered him when putting on his shoes and performing physical activities. He presented no known comorbidities.

On physical examination, the patient presented raised hyperkeratotic plaques, with a rough/warty and friable surface, painful to minimal trauma and pressure from clothes and shoes. The most elevated plaques varied in size, between 1cm and 4cm in their longest axis.

Around the most elevated lesions, there were small keratotic dark red plaques, with segmental distribution, extending from the lower third of the left leg to the instep and ipsilateral hallux. There was no difference in circumference between the two legs. Dermoscopy was necessary for the diagnostic elucidation, showing a lesion with an important keratotic component and a discreet whitish veil, interspersing dark red/ black venous lakes, with small hemorrhagic crusts and peripheral erythema (Figure 2).

The patient reported having performed a partial excision of the lesion ten years ago, but there was local recurrence.

Due to the history of recurrence, we opted for deep surgical excision (even muscular fascia), in two stages. Initially, the most extensive lesion was excised, with an angled allowing the primary closure, which resulted in a Y scar, and closure with moderate tension due to little skin mobility at the site (Figure 3).

We started performing central pulley sutures, for a better approximation of the edges, and then we used simple internal and external sutures, with nylon 3.0.

Primary closure allows faster recovery and less postoperative morbidity. Whenever possible, it should always be the first surgical option.

Histopathology showed ectasia and proliferation of vessels in the superficial and mid-dermis, surrounded by hyperplastic epidermal squamous epithelium, without atypias (Figure 4).

Corroborating clinical, dermoscopic and histopathological data, we concluded that it was angiokeratoma circumscriptum, the rarest variant among angiokeratomas.

The patient presented good healing of the surgical wound and returned for excision of the other minor lesions, near the major lesion.

DISCUSSION

Angiokeratomas are vascular lesions defined as one or more dilated vessels of the papillary dermis, accompanied by acanthosis/hyperkeratosis of the epidermis.[4] The worldwide

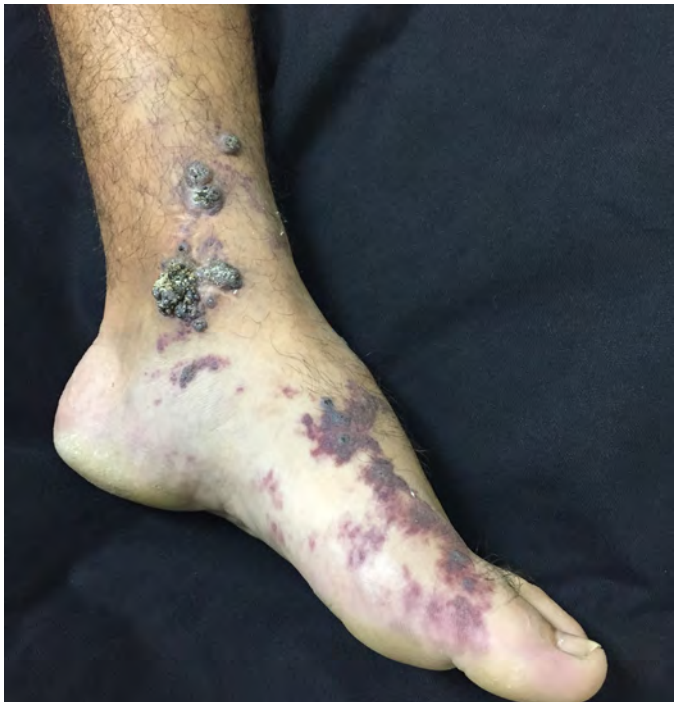

Figure 1: Elevated, keratotic, and friable dark red plaques

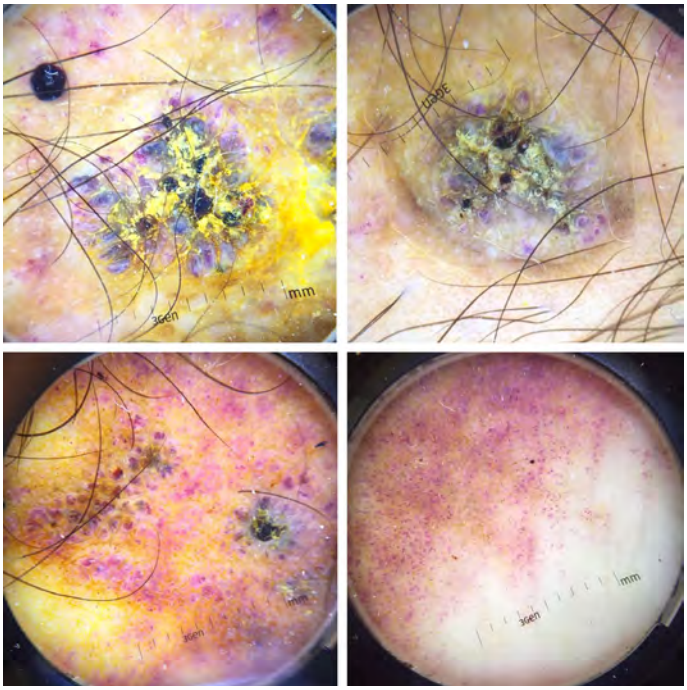

Figure 2: Dermoscopy shows keratosis, with a discreet whitish veil, interspersed with dark red/ black venous lakes, with small hemorrhagic crusts and peripheral erythema

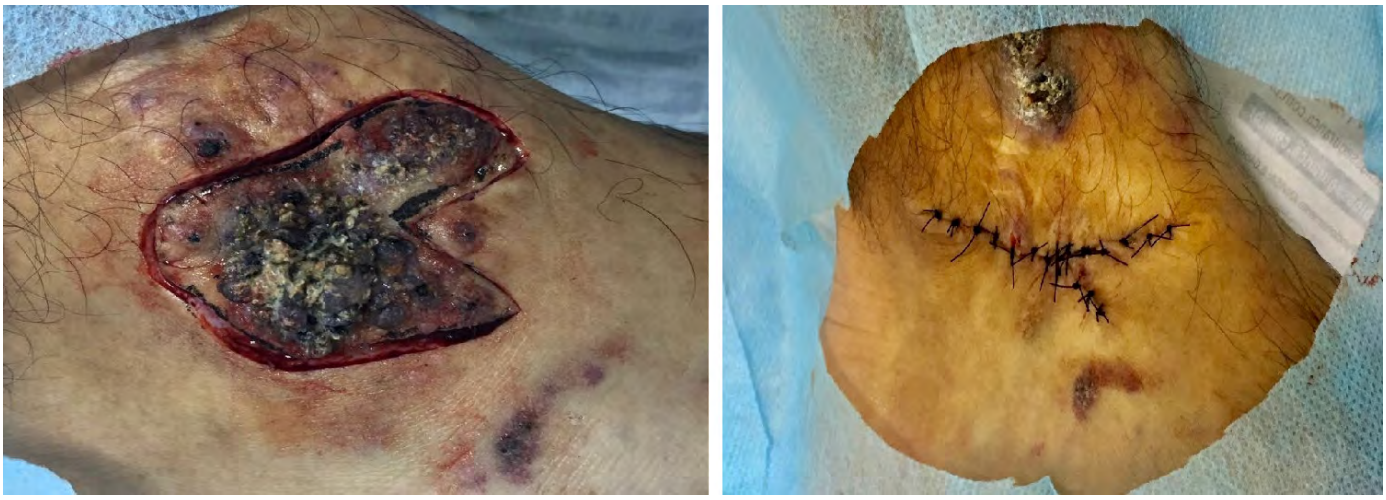

Figure 3: Deep surgical excision

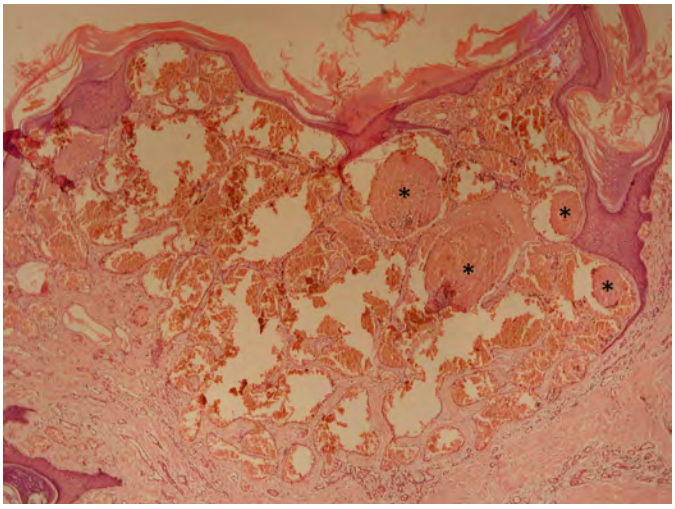

Figure 4: *Ectasia and proliferation of vessels in the superficial and middle dermis, surrounded by hyperplastic epidermal squamous epithelium, without atypias (Hematoxylin & eosin 40x)*

prevalence is 0.16%, affecting slightly more men.[4] Angiokeratoma circumscriptum is considered the rarest variant. It most frequently affects the lower limbs, unilaterally, or asymmetrically distributed between the two members, [4] but it can also occur on the thighs, buttocks or other parts of the body.[6] They are papular and/or nodular lesions that, over time, coalesce and become verrucous, hyperkeratotic plaques, in zosteriform distribution.[1,3,4]

In most cases, they are already present at birth, but they can develop in childhood or adolescence and even during adulthood.[5,6]

Our patient presented the classic picture of angiokeratoma circumscriptum: men, lower limb lesion present since birth, with progressive growth until adulthood, becoming symptomatic. The pathophysiological mechanism of the formation of these lesions is still unknown.[4,5,6,7] Initially, there is vascular ectasia of the papillary dermis, and epidermal changes occur secondarily.

Some authors suggest that the development of hyperkeratosis may be associated with the expression of metalloproteinase-9 (mmp9) in the lesion.[4,6] Changes in local hemodynamics, such as trauma to the capillaries in the papillary dermis, can cause the appearance of telangiectasias in the papillary dermis with hyperkeratosis and acanthosis in the epidermis. There are also reports of the expression of VEGF and its receptors (VEGFR-1 and 2) in the dilated capillary endothelial cells of these lesions. VEGF is an angiogenic growth factor. Of its receptors, VEGFR-1 is involved in cell migration and vascular maintenance; VEGFR-2 acts primarily in the regulation of mitosis and cell proliferation, but its exact role has not yet been precisely elucidated.[6]

Some authors consider, in addition to trauma, pregnancy, subcutaneous hematomas, and tissue hypoxia as other possible triggering factors.[5]

Angiokeratoma circumscriptums may coexist in association with Klippel-Trenaunay syndrome (port-wine stain, venous and lymphatic malformation, and soft tissue hypertrophy).[4,5,7,8] It may also be associated with Cobb syndrome, nevus flammeus, cavernous hemangioma, and traumatic arteriovenous fistula.

Our patient presented no known risk factors or association with other types of lesions.

The diagnosis is primarily clinical and confirmed by histopathology, which shows hyperkeratosis, papillomatosis, and acanthosis, with the proliferation of vessels limited to the papillary dermis.[7,8,9] The histopathological differential diagnosis is made with verrucous hemangioma, which consists of congenital and localized vascular malformation, but involving the reticular and subcutaneous dermis. Angiokeratoma circumscriptum consists of vascular dilation without vessel proliferation. On the other hand, verrucous hemangioma is considered a hyperplastic tumor, with mesenchymal cell proliferation tending to form capillaries.

Dermoscopy assists in the diagnosis, showing reddish lacunae and a whitish veil, covered by whitish scales and/or hematic crusts. However, dermoscopy does not allow todifferentiate a verrucous hemangioma from a circumscribed hemangioma due to the difficulty in estimating the depth of the lesion.

It is important to remember that, clinically, it can mimic a malignant melanoma.[7,10] Cutaneous tuberculosis, deep mycoses,

viral warts, and other lesions that show a linear growth pattern should also be considered as clinical differential diagnoses.[7]

Corroborating clinical, dermoscopic, and histopathological data, we closed the diagnosis of angiokeratoma circumscriptum, the rarest variant among angiokeratomas.

Angiokeratoma does not regress spontaneously. Small injuries can be treated with electrocautery, curettage, or cryosurgery. More extensive lesions require deep surgical excision and, depending on the size of the defect, direct closure, flap, or graft. Other options include CO2 or argon laser.[4,5,7,10]

The rarity of this entity in the world literature motivated the report of this case.

Our patient presented the classic clinical, dermoscopic, and histopathological features of the angiokeratoma circumscriptum.

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Adjuvant oral minoxidil for the treatment of alopecia areata refractory to Janus kinase inhibitors

Tratamento adjuvante com minoxidil oral para tratamento de alopecia areata refratária a inibidores de JAK

DOI: http://www.dx.doi.org/10.5935/scd1984-8773.20201211512

ABSTRACT

Janus kinase inhibitors have changed the therapeutic paradigm of severe alopecia areata therapy. Some patients are refractory to dosage escalating. In this article, we describe the applicability of adjuvant oral minoxidil therapy.

Keywords: Alopecia; Alopecia Areata; Hair Janus Kinases; Minoxidil

RESUMO

Inibidores de Janus quinase mudaram o paradigma terapêutico de alopecia areata grave. Alguns pacientes são refratários ao aumento da dosagem. Neste artigo, descrevemos a aplicabilidade da terapia adjuvante com minoxidil oral.

Palavras-chave: *Alopecia; Alopecia areata; Cabelo; Janus Quinases; Minoxidil*

While Janus kinase (JAK) inhibitors have changed the therapeutic landscape of severe alopecia areata (AA), not every patient with AA responds to JAKi, and other treatment challenges remain: (1) Some patients require increased doses of JAK inhibitor to achieve hair regrowth; (2) Disease relapse can occur despite ongoing treatment; (3) If disease relapse occurs after treatment discontinuation, the same hair regrowth as occurred with initial treatment may not occur with retreatment.

In 1987, a study of oral minoxidil, 5mg twice daily, for the treatment of AA showed that 20% of patients achieve cosmetically acceptable hair growth.1 Recently, we observed that tofacitinib used in combination with oral minoxidil may be more efficacious than tofacitinib monotherapy in patients with severe AA.2 Here we present 3 patients with AA undergoing monotherapy with tofacitinib or ruxolitinib in which there was no efficacy or waning efficacy; in each case, adding (adjuvant) oral minoxidil (AOM) produced an excellent response (Figures 1 and 2).

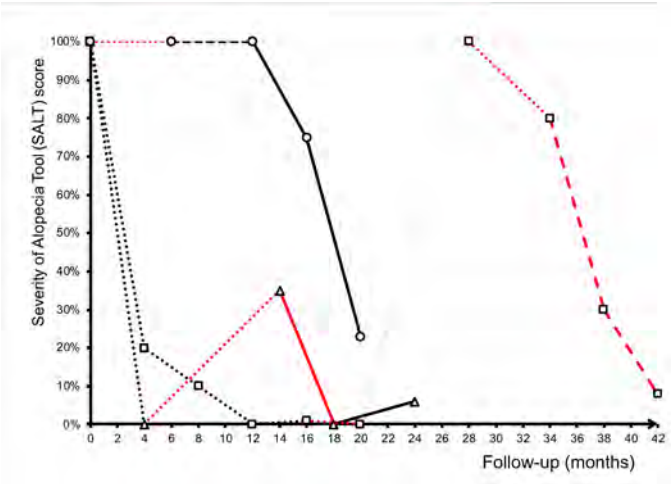

Figure 1: Longitudinal Severity of Alopecia Tool (SALT) scores of patients undergoing Janus kinase (JAK) inhibitor treatment.
Dotted lines: prior to and after starting adjuvant oral minoxidil (AOM). **Continuous lines:** minoxidil 2.5mg twice daily. Dashed line: minoxidil 2.5mg daily. Red lines: higher dose (tofacitinib 15-20mg per day in divided doses). Black lines: standard dose (tofacitinib 5mg twice daily or ruxolitinib 25mg twice daily [short dashes]). Light gray line: discontinuation of prescription. The indication for AOM was: Disease relapse during treatment with JAK inhibitor (Δ), decreased retreatment efficacy (), and poor response to JAK inhibitor monotherapy (O). After starting AOM, hair regrowth is apparent (illustrated by decreasing SALT scores).

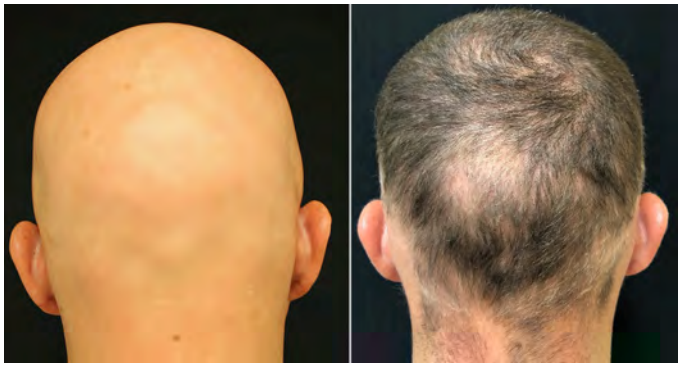

Figure 2: Alopecia areata unresponsive to JAK inhibitor monotherapy. Left: After 6 months of ruxolitinib 25 mg twice daily, Severity of Alopecia Tool (SALT) score was 100% (same as prior to starting ruxolitinib). Right: Nine months after starting adjuvant oral minoxidil (AOM), SALT score was 23%.

In some patients who are refractory to JAKi monotherapy, AOM may offer a solution. In our experience, the response to adjuvant treatment is typically seen 3-6 months after initiation of AOM (2,5mg, once or twice daily). Combination therapy may improve efficacy of JAKi, thereby limiting the need to escalate dosage, which is costly and potentially increases the risks for adverse effects. Additional studies will be important to better understand the optimal use of oral minoxidil in combination with JAKi.●

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Case report

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Filling with hyaluronic acid and transcutaneous blepharoplasty in stable systemic sclerosis

Preenchimento com ácido hialurônico e blefaroplastia transcutânea em esclerodermia sistêmica estável

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ABSTRACT

Systemic sclerosis is a disease of unknown cause, is a rare pathology that, when not treated in time, produces severe damage to the facial aesthetic anatomy causing a significant impact on the quality of life. The case of a 54-year-old woman, with a history of systemic sclerosis of 25 years of evolution, and who was stable from her disease over four years ago. The patient consults for resolution of her facial deformity, which is why she proceeds to perform minimally invasive low-risk procedures such as transcutaneous blepharoplasty and fillings with hyaluronic acid obtaining aesthetically adequate results.

Keywords: Blepharoplasty; Hyaluronic acid; Scleroderma, diffuse

RESUMO

A esclerose sistêmica é uma doença de causa desconhecida, que se caracteriza pelo espessamento da pele. Trata-se de uma patologia rara que, quando não é tratada a tempo, produz um dano grave na estética facial causando um grande impacto na qualidade de vida. Relatamos o caso de paciente feminina, 54 anos, com esclerose sistêmica há 25 anos, referindo estabilidade da doença há mais de quatro anos. A paciente se apresentou à consulta com queixa de deformidade facial. Foi submetida a procedimentos minimamente invasivos e de baixo risco - blefaroplastia transcutânea e preenchimento com ácido hialurônico - obtendo resultados esteticamente adequados.

Palavras-chave: *Blefaroplastia; Ácido hialurônico; Esclerodermia difusa*

INTRODUCTION

Systemic sclerosis (SS) is a disease of the connective tissue that is characterized by an excessive deposit of collagen and other substances in the extracellular matrix, producing cutaneous sclerosis and damage to the microvasculature of the skin and internal organs.[1-4] It predominantly affects women, with a women:men ratio of 4:1.[5] The most common symptoms include Raynaud's phenomenon, polyarthralgia, dysphagia, heartburn, edema, skin thickening, and contractures of the fingers.[5]

There are three phases of dermal involvement: initially, there is an edematous phase, which often presents stiff and swollen hands and fingers; the second phase, called indurative,

is characterized by thickening and hardening of the skin (sclerodactyly and the classic expressionless face); and finally, there is an atrophic phase.[5,6]

SS is classified as limited (LSS), diffuse (DSS), and sine scleroderma (without scleroderma - ssSS). In cases of LSS (CREST syndrome: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), patients develop skin tension on the face and in the distal portion of the elbows and knees. They may also have gastroesophageal reflux disease.[6,7] In DSS, there is great diffuse skin involvement; patients present Raynaud's phenomenon and gastrointestinal complications. This type of SS tends to evolve rapidly. Interstitial lung disease and scleroderma renal crisis are the main complications.[8-10] In ssSS, patients have antibodies related to SS and visceral manifestations of the disease, but no skin involvement.9

Its incidence is <10 per 1 million per year, and its prevalence is <150 per 1 million in northern Europe and Japan. In the United States, Canada, southern Europe, and Australia it has an incidence of >10 per 1 million per year and prevalence estimates of >150 per 1 million.[11]

The term scleroderma was introduced by Gintrac in 1847 and arose from the importance of the skin's participation in vascular disease and fibrotic changes.[12] Currently, the term scleroderma refers to the skin involvement of patients. Every patient with morphea has scleroderma (cutaneous fibrosis), but not every patient with SS has scleroderma, which is why the term scleroderma should not be used as a synonym for systemic sclerosis.[5]

The exact pathophysiology of scleroderma is unknown. It is considered to be secondary to an autoimmune reaction that causes localized collagen overproduction. In some cases, it has been linked to exposure to chemicals. Genetic and infectious factors were involved as possible causal agents.[5]

Facial impairment of systemic sclerosis and morphea is associated with oral complications, and aesthetic changes strongly affect the patient's self-image and quality of life.[13-15]

CASE REPORT

We present the case of a 54-year-old woman with a history of hypothyroidism, controlled with levothyroxine 50mg, severe depression, treated with escitalopram 10mg, and a diagnosis of SS with 25 years of evolution. She was being treated with tacrolimus 1.5mg every 12 hours, sirolimus 1.5mg per day, and methylprednisolone 4mg per day.

On physical examination, she presented atrophic skin, not very hard, without dyschromia, and also severe atrophy of the malar and zygomatic fats and the cheek area. We also observed, secondary to this loss of facial volume, a great herniation of the lower eyelid fat compartments, and microstomy, resulting in the classic aspect of mask-like appearance in this type of patients (Figure 1).

Procedure: Local anesthesia without vasoconstrictor was performed, followed by a transcutaneous incision 0.5cm in the area of greater fat extrusion in the lower eyelid. We removed part of the exuberant fat bags one centimeter below the eyelid, controlling the almost nonexistent bleeding and suturing the lesion with a single stitch using 6-0 monocryl, which was removed after seven days. We decided on this approach through the skin due to the exuberance of the bags, as it was the easiest and least complicated technique, without risk of ectropion (Figure 2).[16,17]

One week later, filling with high G prime or high-density hyaluronic acid (HA) (Voluma, Allergan, Guarulhos, Brazil) was applied with a cannula 21g in a linear retrograde fan pattern in the supraperiosteal plane in the malar, zygomatic, and in Bichat's fat, totaling 4ml of HA per cheek (Figure 3).[19-23]

Then we apply 1ml of low-density HA (Volbella, Allergan, Guarulhos, Brazil), using a with needle 30G, to perform linear retroinjection in the perioral wrinkles and lip contour. Finally, we applied medium-density HA 1ml (Volift, Allergan,

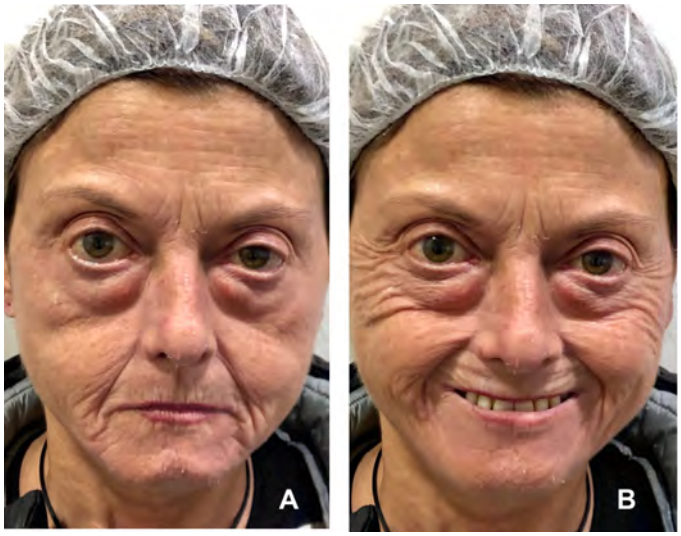

Figure 1: Physical examination of the patient: **(A)** At rest. **(B)** In dynamics

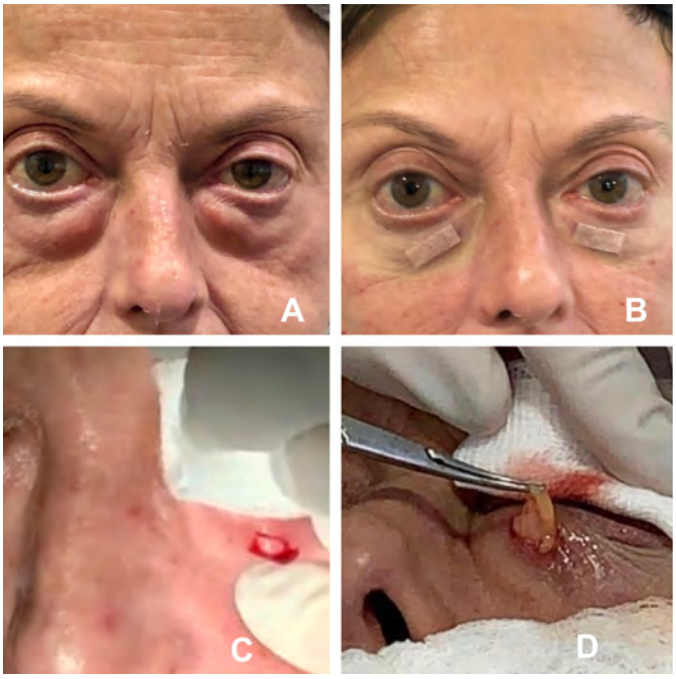

Figure 2: Pre and immediate postoperative, skin incision and visualization of infraorbital fat

Guarulhos, Brazil), with a needle in small points in the lip vermilion to improve the turgor. [24,25]

A very suitable aesthetic result was obtained, significantly improving the quality of life of this patient (Figures 4 and 5).

DISCUSSION

Recent studies cite that injections of HA, a non-sulfated anionic glycosaminoglycan widely distributed in all connective tissues, epithelial and neural, would be a possible treatment for cutaneous fibrosis.[18,19] It is believed that hyaluronic acid would be a valid therapy in patients with scleroderma due to its filler properties, in addition to its ability to retain water, smoothing, and moisturizing the skin.[20,21] Also, HA has been shown to induce the production of type I collagen in the dermis, which could explain its long-lasting effect.[22]

Recently, the group led by Guggino included ten women between 18 and 70 years old, with systemic sclerosis.

Each patient was treated with three injections of HA and platelet-rich plasma every 15 to 20 days. All patients were assessed monthly, at three and 24 months after the end of the treatment, regarding mouth's opening, freedom of movement of the lips, and skin elasticity. The group observed that eight patients (80%) showed higher mouth's opening and increased thickness of the upper lip since the first month of follow-up, maintaining these results after two years of initial control.

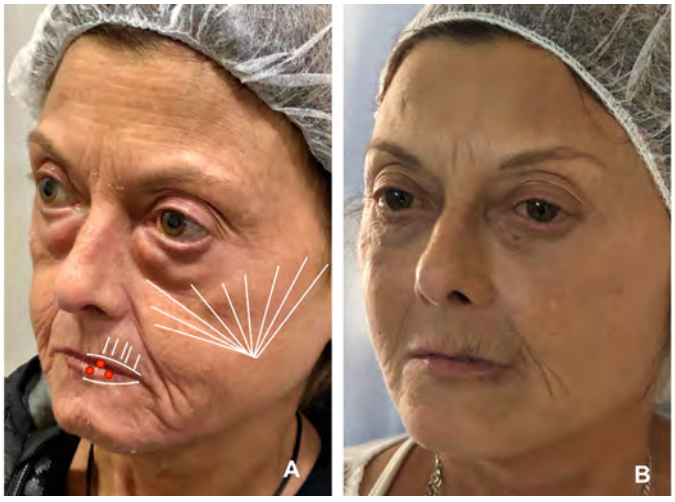

Figure 3: Areas treated with hyaluronic acid

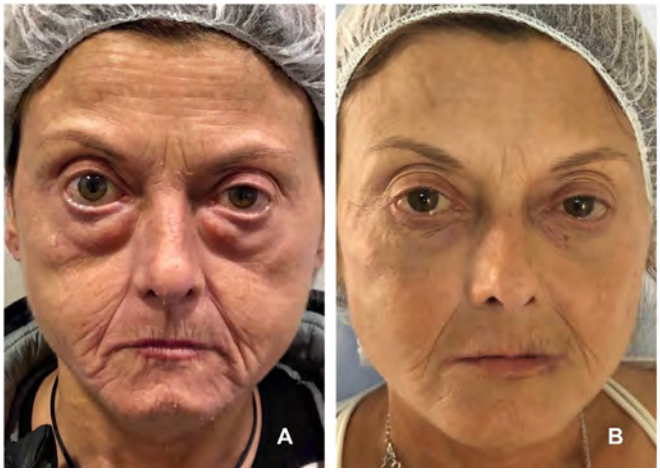

Figure 4: Areas treated with hyaluronic acid. Before and after

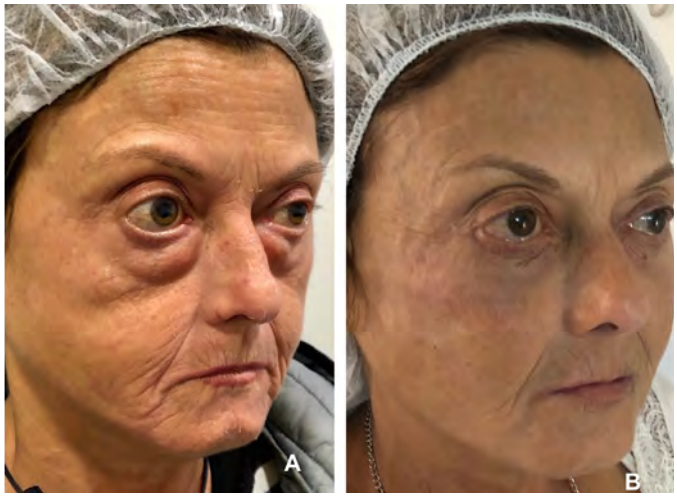

Figure 5: Pre and post oblique

Another potential filler could be the autologous fat. Autologous fat lipotransfer for soft tissue filling has been described as a well-established aesthetic, and plastic surgical technique.[14] Patients with stable scleroderma who have been injected with autologous fat have been reported.[13] It is believed that the fat grafting may have tissue regenerative properties, not only serving as a filler, thus postulating that in the fat there could be stem cells, fibroblasts, and endothelial cells that would decrease fibrosis.[13,14]

There is no consensus in the literature on the application of fillers and minimally invasive surgery in patients with systemic sclerosis. Thus, we suggest and consider that the stability of the systemic condition for more than two years (clinical and laboratory stability) should be sufficient to allow the use of HA or autologous fat in these patients. Note that, before using any filler, you must confirm the stability of the disease, verify and all medications in use by the patient (immunosuppressants, anticoagulants, etc.), and update the laboratory tests (complete blood count, platelet count, hepatitis C and B, HIV, and quantiferon-TB).[16]

CONCLUSIONS

Minimally invasive procedures, such as transcutaneous blepharoplasty and facial filling with HA, can successfully improve the cutaneous cosmetic complications of SS. The appropriate aesthetic result will depend on the experience, technique, and skill of dermatologists and/or plastic surgeons.●

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Case Report

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Inverted T Incision with Osteophyte Removal in The Treatment of Pincer Nail

Incisão em T invertido com remoção de osteófitos, no tratamento da unha em pinça

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ABSTRACT

Pincer nail deformity is characterized by excessive transverse over curvature of the nail. A 58-year-old woman came with a complaint of pincer nail accompanied by swelling and pain in the last 1 month due to frequent use of narrow shoes. We performed a surgical intervention indicated to treat pain, inflammation, interference with wearing shoes, and cosmetic embarrassment using an inverted T incision method with osteophyte removal. This case showed that the surgical approach did not require a long time to be conducted, presenting brief healing time, minimal pain, and excellent cosmetic outcome.

Keywords: Osteophyte; Ambulatory surgical procedures; Nails, malformed

RESUMO

A deformidade da unha em pinça é caracterizada por excessiva curvatura transversal da unha. Uma mulher de 58 anos apresentou-se com queixa de unha em pinça acompanhada de edema e dor no último 1 mês devido ao uso frequente de sapatos estreitos. Foi realizada uma cirurgia para tratar dor, inflamação, interferência no uso de calçados e cosmético, utilizando o método de incisão em T invertido com remoção de osteófitos. Este caso mostrou que a abordagem cirúrgica não foi demorada, apresentando curto tempo de cicatrização, dor mínima e excelente resultado cosmético.

Palavras-Chave: *Osteófito; Procedimentos cirúrgicos ambulatoriais; Unhas mal formadas*

INTRODUCTION

Pincer nail deformity is a nail disorder of the hands and feet characterized by an excessive transverse over the curvature of the nail, which is caused by osteophyte formation in the distal phalanx.[1] Cornelius and Shelley first described pincer nail deformity in 1968 as a transverse distal over the curvature of the nail.[2] Based on its etiology, there are four distinct types of pincer nail: hereditary pincer nails, posttraumatic pincer nails, pincer nails in arthropathic disorders, and pincer nail affecting a single nail.[3] Foot alterations because of narrow shoes or osteoarthritis are reported to cause pincer nails.[4] A pincer nail compresses the nail bed leading to pain during walking or exercising as well as cosmetic problems.[5] Pain may arise due to the embedding of the pincer nail in the lateral nail folds and nail bed, which becomes more pronounced distally.[6] Several conservative and surgical treatment methods have been suggested to correct pincer nail deformities.[7] However, there is still no established standard method for treating pincer nail deformity currently.[7]

Pincer nail is rarely found and reported in our region. Also, when a diagnosis is established, patients are often reluctant to undergo surgical correction. Here, we report the first case of pincer nail deformity surgical correction with osteophyte removal in our center.

CASE REPORT

A 58-year-old woman presented to the Outpatient Department of Dermatology Hasanuddin University Hospital, Makassar, South Sulawesi, Indonesia, with a complaint of pincer-shaped right toenail accompanied by swelling and pain since one month before admission. Initially, the patient reported she had noticed the nail deformity since two years ago; however, at that time, there were no complaints, so the patient did not seek treatment.

There was a history of trauma to the right toenail due to the frequent use of narrow shoes. The patient had diabetes and routinely consumed metformin twice a day in the last five years. Also, the patient had a history of uncontrolled hypertension. The patient denied having a history of similar complaints before or in her family.

The patient was otherwise in good general condition. Dermatological examination showed nails clamping towards the medial and edema on the first finger of the right foot (Figure 1A). Considering the history and physical examination, we decided to perform corrective surgery using the inverted T incision method.

The surgery was conducted under local digital block anesthesia using 1% lidocaine after disinfection with povidone-iodine. A digital tourniquet application was applied to prevent bleeding during the procedure. The first step was to perform a total nail avulsion by using iris scissors and nail splitters to separate the nails from the nail bed (Figure 1B). Precaution was taken not to injure the nail bed. In the second step, an inverted T incision, starting from the medial nail bed extending to the hyponychium down to the bone, was made using a sharp knife (blade #11) to explore the distal phalanx and expose the osteophyte (Figure 1C). In the third step, after the nail bed was cut along the previously determined incision line, osteophytes were found on the surface of the distal phalanx (Figure 1D) and were subsequently removed (Figure 1E). In the fourth step, the nail bed was sutured, and the medial nail bed (which was widened by the incision) was sutured using polyglactin 4-0 (Figure 1F). Both sides of the nail bed were sutured separately to the lateral borders (Figure 1G). This suture was maintained for three weeks to keep the nail bed stretched over the bone. A significant improvement on the nails was observed after 6 months.

DISCUSSION

The over curvature of the nails is commonly called pincer nails, tubed nails, or trumpet nails.[8] The risk of pincer nails is higher in the big toenails compared to the fingernails, and its incidence rate is two times higher in women than in men.[4] Pincer nail deformity should be diagnosed and treated because

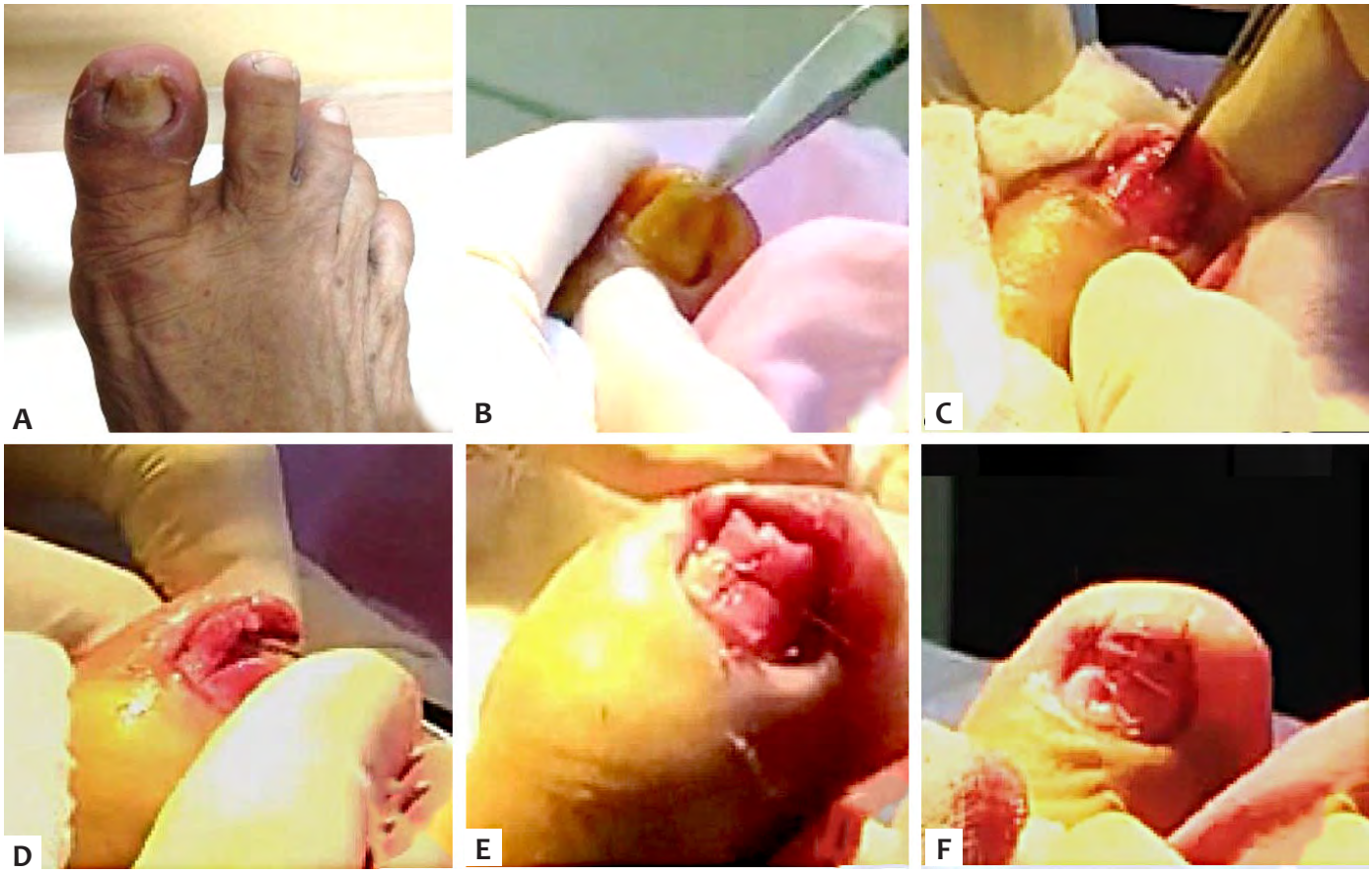

Figure 1: Pincer nail on the patient's right big toe **(A).** Total nail avulsion **(B).** Inverted T incision starting from the medial part of the medial nail plate and extending to the hyponychium **(C).** Exploration of the dorsal aspect of the distal phalanx **(D).** Removal of osteophytes in the dorsal phalanx **(E).** Suture in the medial part of the nail bed after removal of osteophytes **(F).** Suture on both sides of the nail bed at the lateral edges **(G).**

it affects not only the appearance but also the function of the digit and the quality of life due to the pain it causes.[9] Cosmetic results of pincer nail surgery have become more critical because of the increasing demand for nail preservation and excellent aesthetic outcome.[10] Surgical methods include nail avulsion, total or partial excision of the nail bed, phenol matrixectomy of the lateral matrix horns, destruction of the matrices by electrocauterization, removal of osteophytes, skin or mucosal grafting of the nail bed, zigzag nail bed flap method, and others.[11]

As excessive osteophyte and narrow nail bed are the underlying factors of the pincer nail, removal of osteophyte and widening of the nail bed are expected to provide an ideal anatomic structure for the healthy growth of the future toenail.[3] Inverted T incision is the method of choice that can be used in high-risk groups, including elderly patients over 70 years old and those with diabetes mellitus, chronic kidney disease, and/or peripheral vascular disease because this method is less invasive than the zigzag nail bed flap method.[2]

CONCLUSION

Correction of pincer nail deformity using the inverted T incision approach is a simple and effective procedure because of shorter operating time, reduced pain during surgery, excellent functional and aesthetic outcome.●

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Electron beam radiotherapy adjuvant to recalcitrant giant keloid surgery in the ear

Radioterapia com feixe de elétrons adjuvante à cirurgia de queloide gigante recalcitrante na orelha

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ABSTRACT

Isolated keloid treatment has variable and often unsatisfactory results. The combination of therapies has proven to be an effective alternative mainly for recalcitrant cases. Surgical excision and immediate postoperative electron beam irradiation is an effective alternative in healing and reducing the recurrence rate of these lesions. The authors describe a patient with recalcitrant bulky keloid who had a good therapeutic outcome.

Keywords: Ear; Keloid; Radiotherapy

RESUMO

O tratamento isolado do queloide apresenta resultado variável e, muitas vezes, insatisfatório. A combinação de terapêuticas tem se mostrado uma alternativa eficaz, principalmente para os casos recalcitrantes. A excisão cirúrgica e a irradiação no pós-operatório imediato com feixe de elétrons é uma alternativa efetiva na cicatrização e redução da taxa de recidiva dessas lesões. Os autores descrevem um paciente que apresentava queloide volumoso recalcitrante que obteve bom resultado terapêutico.

Palavras-chave: *Orelha; Queloide; Radioterapia*

INTRODUCTION

Keloids are benign lesions resulting from a posttraumatic fibrous proliferation of the skin. They result from excessive deposition of collagen in the extracellular matrix during the healing process. Morphologically, they are characterized by cellular hyperplasia due to the presence of intrinsically normal polyclonal fibroblasts that respond to an abnormal extracellular signal. Such injuries can be disfiguring and cause physical discomforts such as pain, burning, and itching. Also, they can restrict movement and form local fistulas after repeated infections and, consequently, affect the patient's quality of life.[1, 2]

Isolated surgical treatment has a high recurrence rate, around 50-80%, which makes the use of adjuvant therapies necessary. The most used are cryotherapy, laser therapy, compression, and intralesional injection of corticosteroids, with variable results. Currently, a treatment established in resistant or refractory keloids is surgical excision followed by electron beam radiothe-

Case report

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rapy (RT). Recurrence rates for the first year are as low as 10% in some cases, and a typical protocol is excision followed by the first radiotherapy session, with ten or more subsequent sessions. Dosage and timing differ between teams and institutions. [2,3]

The use of electron RT adjuvant to surgical treatment is based on the fact that, once the keloid is formed, it is not radiosensitive. Under these circumstances, the fibrous tissue will undergo little or no change with irradiation. However, fibroblasts from recent scars are highly radiosensitive.[1,3] We report the case of a recalcitrant keloid in which surgical treatment with adjuvant electron beam RT was employed successfully.

CASE REPORT

A 31-year-old man presented a large keloid lesion, approximately 15cm in the longest axis, originating from the left auricle and occupying the entire ipsilateral retroauricular portion (Figures 1 and 2). The condition began when he was 11 years old after trauma. The patient reported that he had already undergone several treatments, including five primary closure surgical approaches, two electrocoagulation surgeries and secondary intention closure, and beta-therapy after one of the surgical approaches at 14 years of age. Among the surgical procedures, he performed infiltrations with intralesional corticosteroids, and, despite the numerous treatments, he presented recurrence with progressive growth. In April 2018, he underwent a new surgical approach with a total lesion excision (Figure 3).

We opted for therapeutic complementation with electron beam RT, which started in the immediate postoperative period. The parameters used were: electron beam generated by a linear accelerator, 9 MeV energy (millions of electron volts = electron beam energy unit), 208 um/time, 100 source-to-surface distance (SSD), use of cone 10 for field delimitation, 100 cm source-to-surface distance, and daily dose of 200 centiGrays (cGy). Ten applications were performed, with a total dose of 2,000 cGy, and the sessions were distributed over two weeks, daily, except on weekends.

As an adverse event, the patient presented with beard and hair alopecia in the irradiated area, with complete repilation after the end of the sessions. The patient remains in follow-up, with good aesthetic and functional results and no evidence of relapse after 1 year of therapy (Figure 4).

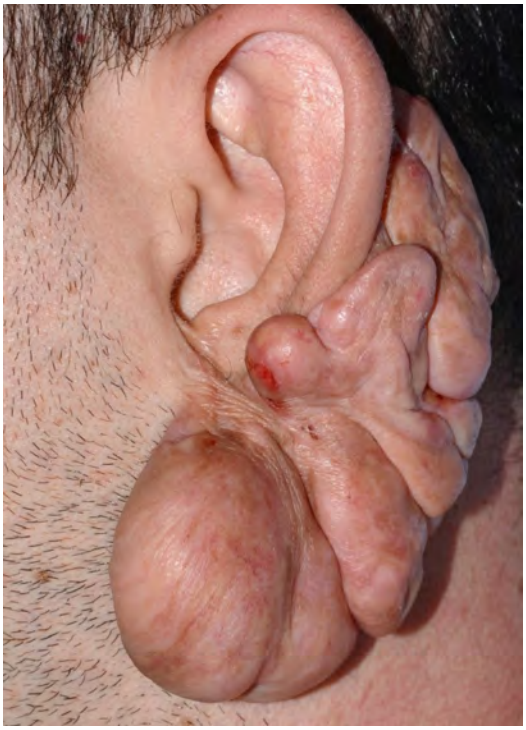

Figure 1: Keloid injury in the left auricle

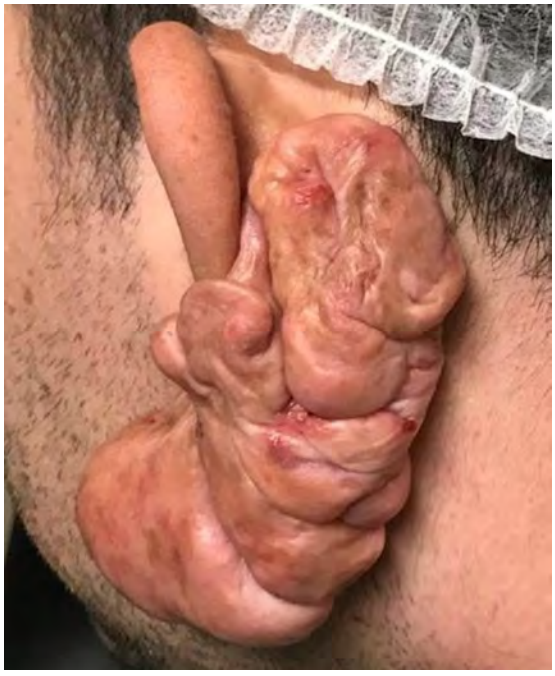

Figure 2: Keloid injury in the left auricle

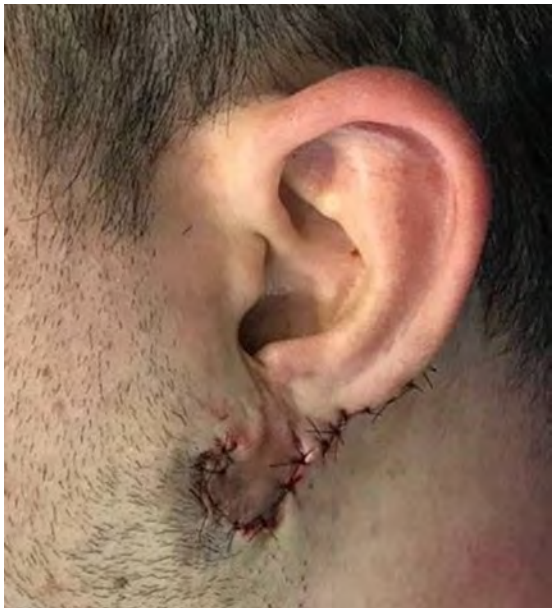

Figure 3: Immediate postoperative

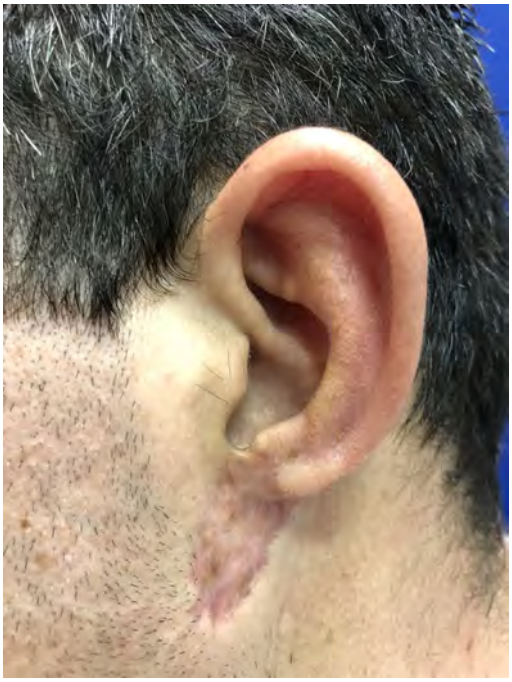

Figure 4: Result 1 year after surgical and radiotherapy treatment

DISCUSSION

There are several treatments available for keloids, and all of them alone have high recurrence rates, including surgical treatment that presents rates close to 100% in some studies. Among the adjuvant treatments employed, radiotherapy is highly effective, less likely to recur, and one of the primary forms used are brachytherapy and electron beam therapy.[1-5]

The biological action of irradiation on fibroblasts is inhibition of proliferation and stimulation of differentiation of these cells.[6]

Adjuvant RT modalities for operated keloids are: conventional X-ray,7 beta-therapy,1 single dose RT,8 and electron beam RT.9 Electron beam RT is superior to traditional X-ray irradiation for the treatment of keloids due to better tissue dose distribution.[7]

There is no consensus as to the best modality to be used or the total dose to be employed. Studies of meta-analysis and systematic review indicate that the most effective total doses of radiotherapy would be between 20 and 40 gray (Gy) (in the reported case the total dose was 20 Gy) and that there is proximity to recurrence rates between brachytherapy (12% in one year) and electron beam therapy (9% in one year), but this would have fewer adverse events such as hyperchromia and telangiectasia.[1- 5]

A comparative study between electron beam radiotherapy and beta-therapy following keloid surgery with 10-year follow-up showed better electron beam efficacy (77% good and optimal for electron therapy versus 46%). % for beta-therapy) and this result is attributed to better radiation dose distribution in the tissues with the electron beam.[1]

Among the RT modalities, the electron beam is the only one that allows a more homogeneous distribution, considering the irregularity of the lesion depth. When the electron beam comes from linear accelerators, a better energy distribution occurs, being more suitable for each thickness to be irradiated.10

The association of surgery and radiotherapy with the electron beam in the immediate postoperative period proved to be a well-tolerated therapeutic modality, with minimal undesirable events, and no, corroborating some cases in the literature. ●

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Comments on sequential Jessner's + 35% TCA peel for the treatment of facial field cancerization

Comentário sobre o peeling sequencial de Jessner + ATA 35% para o tratamento do campo cancerizável da face

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We have read the article by Melo *et al.*[1] with great interest, especially the observation that 78% of patients preferred the medium-depth peel, while only 22% preferred imiquimod. Notably, this study may have underestimated patients' preference for chemical peeling, since the FDA-approved, on-label application for imiquimod is a twice-weekly application for 16 weeks, resulting in a longer, more severe inflammatory reaction (which translates as the patient's experience of "downtime"), relative to the thrice-weekly application for 4 weeks under investigation in this study. A shortened regimen of imiquimod may impact its efficacy, and it is probable that with the on-label application for 16 weeks, a greater proportion of patients may have preferred the chemical peel.

A recent article by Jansen *et al.*.[2] that omitted medium--depth chemical peeling as an option for field therapy showed that field treatment with 5% fluorouracil (5-FU) twice a day was superior to imiquimod three times a week, one treatment with photodynamic therapy, and 3 daily applications of 0.015% ingenol mebutate. In this trial, 5-FU was applied for 4 weeks (package insert recommends 2-4 weeks), and imiquimod was applied in the same off-label regimen used by Melo *et al.*[1]: three times weekly for 4 weeks. In short, imiquimod may not be the most suitable comparator for field therapy of diffuse actinic keratosis.

Another split-face trial further showed that a single application of Jessner's solution plus 35% trichloroacetic acid had similar efficacy to that of a 3-week course of 5-FU at 12- and 32-months follow-up.[3,4] In this study, patients also preferred chemical peeling due to its tolerability and comparatively short downtime.[3,4]

Letter

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The International Peeling Society suggests standardized terminology: wounding agents mixed in the same formula are termed combination chemical peel, and wounding agents applied sequentially, for example, a superficial peel such as Jessner's solution followed by a second wounding agent like trichloroacetic acid (TCA) is termed sequential peel.[5]Another medium-depth peel option for field cancerization is the Brody peel, a sequential peel in which solid CO2 slush (a physical wounding agent) is followed by 35% TCA, with no systemic absorption of chemicals. This peel contrasts the sequential peels described by Monheit, in which Jessner's solution (a superficial peel) is followed by 35% TCA, and by Coleman, in which 70% glycolic acid (a superficial peel) is followed by 35% TCA. The Coleman peel does not seem to have any advantage over the Monheit or Brody peels, as glycolic acid requires neutralization or washing prior to application of 35% TCA.5 The Coleman peel can be a useful alternative for patients who are allergic to salicylic acid (a component of Jessner's solution), for extensive surface area application of Jessner's solution, which may be a risk for salicylism, or in a clinical setting without access to solid CO2.

Deep chemical peels based on phenol and croton oil might be even more effective in the treatment of field cancerization, given that the depth of penetration extends into the upper reticular dermis. As with any surgical procedure, supervised hands-on training is required for chemical peeling and can be obtained through post-graduate medical training or through specialty societies such as the International Peeling Society (peelingsociety.com).

"I have used my version of the Jessner's - 35% TCA for actinic keratosis and solar damage on many patients for both indications of failure of 5-FU and those patients not willing to put up with the 3 to 4 weeks of topical therapy. Results have been good with the advantage of cosmetic improvement they all appreciate. If they are willing to endure a week of healing, they will enjoy the results." - Gary D. Monheit, M.D.

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