

## Original Article

## Authors:

Gilmayara Alves Abreu Maciel Pereira<sup>1</sup>  
 Diego Leonardo Bet<sup>1</sup>  
 Maria Victoria Suarez Restrepo<sup>1</sup>  
 Vanessa Barreto Rocha<sup>1</sup>  
 Leticia Arsie Contin<sup>1</sup>

<sup>1</sup> Hospital do Servidor Público Municipal de São Paulo, São Paulo (SP), Brazil.

## Corresponding author:

Vanessa Barreto Rocha  
 Rua Castro Alves, 60 - 5º andar  
 Aclimação, São Paulo (SP), Brazil.  
 01532-000  
 E-mail: vanessabarreto.vbr@gmail.com

Received on: 27/03/2020

Approved on: 29/05/2020

Research performed at the Department of Dermatology, Hospital do Servidor Municipal de São Paulo, São Paulo (SP), Brazil.

Financial support: None.

Conflict of interest: None.



# A single blind, randomized clinical trial comparing MMP®, MMP® with 5-FU, and 5-FU intradermal injection for the treatment of idiopathic guttate hypomelanosis: a pilot study

*Ensaio clínico cego randomizado comparando MMP®, MMP® com 5-FU e injeção intradérmica de 5-FU para o tratamento da hipomelanose gutata idiopática: um estudo-piloto*

DOI: <http://www.dx.doi.org/10.5935/scd1984-8773.20201222558>

## ABSTRACT

**Introduction:** Idiopathic guttate hypomelanosis (IGH) is a common photoaging manifestation, with no standard treatment and presenting mixed results to interventions. In Brazil, the use of micro-needling associated with 5-fluorouracil (5-FU) has been proposed to treat IGH.

**Objective:** To compare the use of MMP® (micro-infusion of drugs on the skin) with 5-FU, with MMP® only as micro-needling (with no drugs), and intralesional 5-FU injected with an insulin syringe in the treatment of IGH.

**Methods:** In a single blind randomized clinical trial, we compared the three treatments: MMP® versus MMP with 5-FU and intralesional 5-FU injection for 180 IGH lesions in the forearm of nine patients.

**Results:** After two treatment sessions, 5-FU alone was the most effective treatment, with statistical significance, compared with micro-needling alone. MMP+5-FU efficacy was lower than intralesional 5-FU injection and higher than micro-needling alone, although without statistical significance.

**Conclusions:** The intralesional application of 5-FU was more effective in the treatment of solar leukoderma. The use of a smaller quantity of medication is the great advantage of the MMP + 5-FU technique. Further studies are needed to standardize these techniques.

**Keywords:** Drug delivery systems; Fluorouracil; Hypopigmentation; Skin aging

## RESUMO

**Introdução:** A hipomelanose gutata idiopática (IGH) é uma manifestação comum de fotoenvelhecimento, ainda sem tratamento padrão, apresentando resultados variados às intervenções. Atualmente, no Brasil, o uso de microagulhamento associado ao 5-fluorouracil (5-FU) tem sido proposto para o tratamento da IGH.

**Objetivo:** Comparar três tratamentos, quais sejam: o uso do MMP® (microinfusão de medicamentos na pele) com 5-FU, MMP® apenas para microagulhamento, e com o 5-FU intralesional injetado com seringa de insulina no tratamento da IGH.

**Métodos:** Em um ensaio clínico randomizado e cego, comparamos o MMP® ao 5-FU com: microagulhamento isolado e com 5-FU intralesional por punção para o tratamento de 180 lesões de IGH no antebraço de nove pacientes.

**Resultados:** Após duas sessões de tratamento, o 5-FU intralesional foi o tratamento mais efetivo, com significância estatística quando comparado ao uso de microagulhamento. A eficácia da MMP + 5-FU foi inferior a 5-FU injetável e superior ao microagulhamento isoladamente, embora sem significância estatística.

**Conclusões:** A aplicação intralesional do 5-FU foi mais eficaz no tratamento da leucodermia solar. O uso de menor quantidade de medicamentos é a grande vantagem da técnica MMP + 5-FU. São necessários mais estudos para padronizar estas técnicas.

**Palavras-chave:** Envelhecimento da pele; Fluoruracila; Hipopigmentação; Sistemas de liberação de medicamentos

## INTRODUCTION

Idiopathic guttate hypomelanosis (IGH) is a manifestation of photoaging that occurs mainly on the extensor surface of the forearms and pretibial areas, and which still has no standardized treatment and presents varied response to interventions.<sup>1</sup> The use of micro-needling associated with 5-fluorouracil (5-FU) has been proposed for the treatment of IGH.<sup>2</sup>

5-FU is a pyrimidine analog used in the treatment of many skin diseases. Intralesional infiltration of this medication and its use in the micro-needled area have been used in the treatment of vitiligo.<sup>3,4</sup>

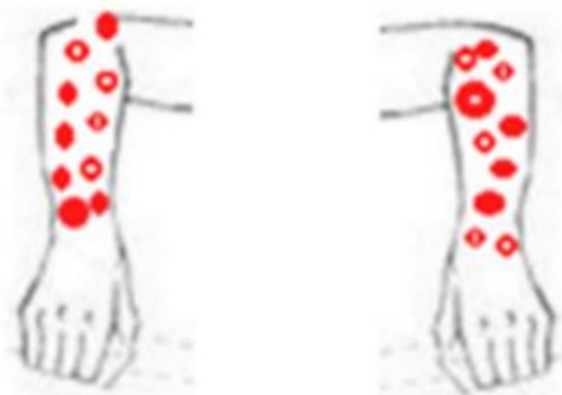
Arbache et al. described repigmentation of IGH with administration of 5-FU via a tattooing machine, using the technique called MMP® (micro-infusion of medications in the skin), with exclusive use by dermatologists.<sup>2</sup>

In the search for an effective therapy for IGH, the current study aims to assess the efficacy of MMP with 5-FU compared to MMP without medication and intralesional 5-FU with a single puncture in the treatment of leukodermas on the forearm.

## MATERIALS AND METHODS

This single-blind randomized clinical trial compared MMP® with 5-FU to micro-needling (MMP® without drugs) and intralesional 5-FU via single puncture with an insulin needle for treatment of 180 IGH lesions on the forearm in nine patients. Ten lesions were treated on each forearm, totaling 180 treated lesions (Figure 1). The treatment technique used on each forearm was selected randomly, each one on six forearms, with a total of 60 lesions. The study was approved by the Institutional Review Board of Hospital do Servidor Público Municipal de São Paulo (CAAE:51923415.1.0000.5442).

Micro-needling was performed with a tattooing machine (Cheyenne, Germany, TRADERM®, SP, Brazil) approved by the Brazilian National Health Regulatory Agency (ANVISA). The cartridge needles used for this protocol, model 7-liner-mt, were immersed in 5-FU or used only for micro-needling (Figure 2). Micro-needling was performed from the periphery towards the center of the depigmented area (2mm or 20 clicks of the machine) until a mild blood dew appeared, a sign that the dermis had been reached. Maximum dose was 50mg/1ml/forearm per session.



RIGHT FOREARM: 1 TO 10

LEFT FOREARM: 11 TO 20

FIGURE 1: Model for marking lesions

Intradermal injection of 5% 5-FU was 0.1ml in each IGH lesion with BD® syringes mounted with a 0.3ml needle, maximum of 50mg/1ml/forearm per session (Figure 3).

All treatments were performed in two sessions with a 30-day interval. Final evaluation was performed at 120 days.

Improvement was evaluated with images of each lesion (standardized clinical photos), classified by a blinded observer using the repigmentation scale (Figure 4). The results were compared using chi-square test (k proportions) or ANOVA, followed by LSD multiple comparison. Statistical significance was set at 5%.

## RESULTS

Mean age was 61 years (range: 49 to 70 years), eight patients were females (89%), two were photo type II, four were photo type III, and three were photo type IV.

Of the 180 lesions, six presented hyperpigmentation as an adverse effect and were excluded from the analysis. Of the 174 lesions, all presented repigmentation, 162 (93.1%) with total repigmentation with normochromia, 12 (6.9%) with partial repigmentation. The great majority of the lesions showed total repigmentation with normochromia for all the treat-

## MMP



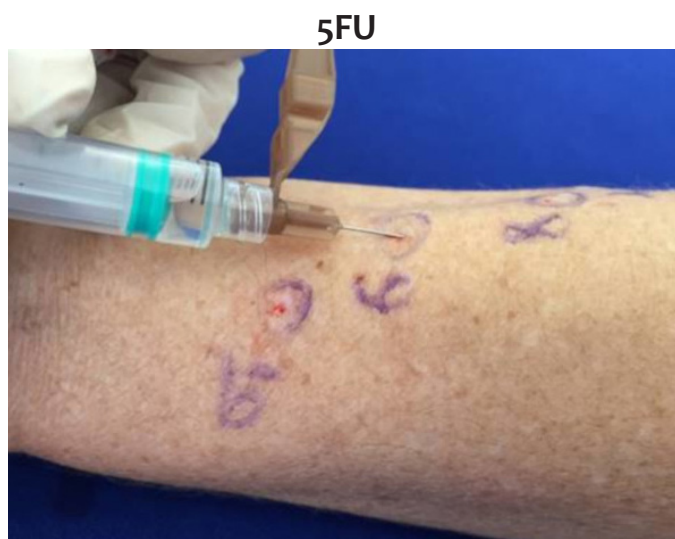
FIGURE 2: MMP technique, using tattooing machine and 7-tipped needle, from periphery to center

ments, with  $57/57=100\%$  for 5-FU,  $50/58=86,2\%$  for MMP, and  $55/59=93,2\%$  for MMP+ 5-FU (Figure 5).

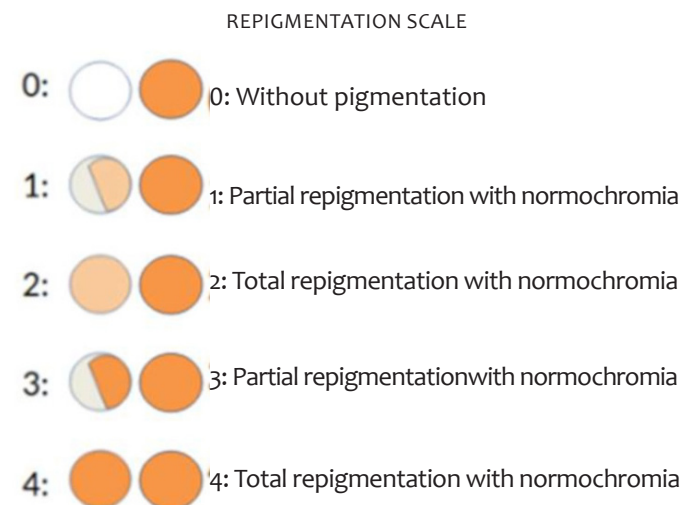
Eight forearms were not submitted to a second session, for different reasons, namely: four reached the treatment target (total repigmentation and normochromia), two of whom using MMP and two MMP+5-FU; three due to erythema in the

lesion sites (one used MMP and two MMP+5-FU); and one due to hyperpigmentation of all the lesions after the first session with 5-FU alone.

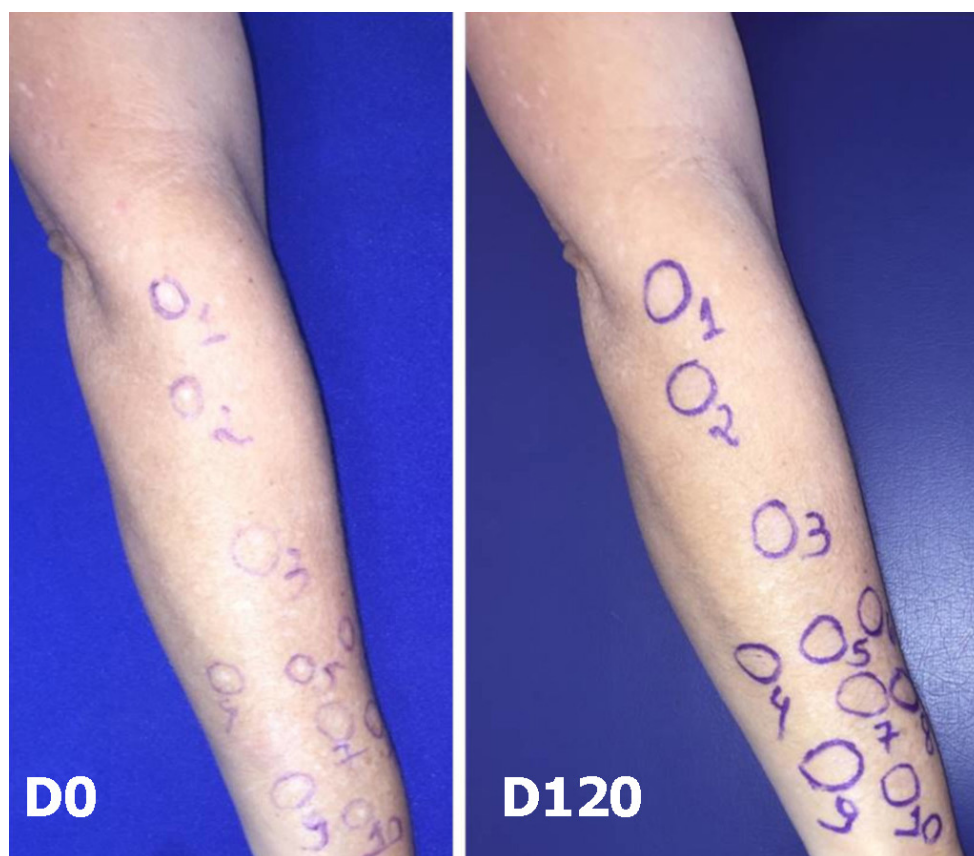
Significant differences were found in the proportions of lesions with total repigmentation with normochromia between the groups treated with 5-FU and with MMP (k proportions



**FIGURE 3:** Intradermal application of 5-FU using insulin needle



**FIGURE 4:** Gradient scale of repigmentation



**FIGURE 5:** Patient 6 on day 0 and post-treatment (D120)

test;  $p=0.014$ ). The proportion was lower in lesions treated with MMP, compared to lesions treated with 5-FU, suggesting greater efficacy with 5-FU injection.

Of the repigmented lesions, 162 (93.1%) presented total repigmentation with normochromia for all the treatments, which was the best result of the five possible results in the repigmentation scale (Figure 4).

Treatment with MMP + 5-FU was the second most effective treatment, although without statistical significance. The lowest efficacy was with micro-needling, which may be due to the lack of use of 5-FU; the treatments with MMP + 5-FU and 5-FU alone showed better clinical and statistical response.

Pain was assessed subjectively by patients, and no statistically significant differences were found between the three treatments. However, pain in the treatment with MMP + 5-FU was considered more intense than in the other treatments.

As for adverse effects such as burning sensation, pruritis, and pain, there were no statistically significant differences between the treatments.

On day 30, one patient presented hyperpigmentation in 10 lesions with the use of intralesional 5-FU. However, on day 120 all the lesions were normochromic.

At the end of the study, six lesions presented hyperpigmentation, one of which had been treated with MMP + 5-FU, two with MMP, and three with 5-FU.

## DISCUSSION

Abd El-Samad and Shaamad, in 2012, were the first to use intralesional 5-FU to treat vitiligo. In 60 patients, there was greater overall repigmentation in the group in which 5-FU was injected, compared to controls ( $p<0.001$ ).<sup>3</sup> Attwa, Khashaba, and Ezzat, in 2019, compared to needling and needling followed by topical 5-FU to treat stable localized vitiligo in 27 patients. Micro-needling followed by topical 5-FU showed a better response than micro-needling alone, with minimal adverse effects.<sup>4</sup>

Arbache S. et al.<sup>2</sup> treated eight patients with IGH lesions, with MMP + 5-FU versus MMP with placebo. Repigmentation of the lesion with MMP + 5-FU was statistically superior to

MMP with placebo (repigmentation with 5-FU = 75.3% versus repigmentation with placebo 33.8%,  $p<0.001$ ).

In our protocol, all 174 lesions (96.7%) presented repigmentation, and none remained achromic after the procedures, which indicates clinical improvement with all three treatments used. No statistically significant differences were observed between the three techniques. However, in the head-to-head comparison, the proportion was statistically lower (k proportions test;  $p=0.014$ ) for lesions treated with MMP for micro-needling (50/58 = 86.2%) compared to lesions treated with 5-FU (57/57 = 100%), suggesting better efficacy of treatment with 5-FU.

After two treatment sessions, intralesional 5-FU was the most effective treatment, with statistical significance, when compared to the use of micro-needling. The efficacy of MMP + 5-FU was inferior to intralesional 5-FU and superior to micro-needling alone, although without statistical significance. The use of a smaller amount of 5-FU (1.175  $\mu\text{g}/\text{cm}^2$  or about 0.00116 ml for each 10 lesions), followed by the technique described by Arbache<sup>2</sup> and the speed and ease of the techniques are the main advantages of MMP + 5-FU compared to injection with insulin needle, which used about 50 mg (1 ml) of medication per session. The adverse effects of 5-FU include pain, pruritis, hyperpigmentation, and burning sensation at the application site.<sup>3,4</sup> Other less frequent reactions include allergic contact dermatitis, pain, tenderness, suppuration, desquamation, and edema.

In our protocol, there were no statistically significant differences between the treatments in relation to pain.

## CONCLUSIONS

Intralesional infiltration of 5-FU was the most effective treatment of localized leukoderma. The use of lower amounts of medications and the technique's speed and ease are the main advantages of the MMP + 5-FU technique. More studies are needed on the maintenance of the level of improvement in the lesions with these three techniques. ●



## REFERENCES

1. Juntongjin P, Laosakul K. Idiopathic guttate hypomelanosis: a review of its etiology, pathogenesis, findings, and treatments. *Am J Clin Dermatol*. 2016;17(4):403-11.
2. Arbache S, Roth D, Steiner D, Breunig J, Michalany NS, Arbache ST, *et al*. Activation of melanocytes in idiopathic guttate hypomelanosis after 5-fluorouracil infusion using a tattoo machine: Preliminary analysis of a randomized, split-body, single blinded, placebo controlled clinical trial. *J Am Acad Dermatol*. 2017;78(1):212-5.
3. Abd El-Samad Z, Shaaban D. Treatment of localized non-segmental vitiligo with intradermal 5-fluorouracil injection combined with narrow-band ultraviolet B: a preliminary study. *J Dermatolog Treat*. 2012;23(6):443-8.
4. Attwa EM, Khashaba SA, Ezzat NA. Evaluation of the additional effect of topical 5-fluorouracil to needling in the treatment of localized vitiligo. *J Cosmet Dermatol*. 2020;19(6):1473-8.
5. Arbache S, Mattos EC, Diniz MF, Paiva PYA, Roth D, Arbache ST, *et al*. How much medication is delivered in a novel drug delivery technique that uses a tattoo machine? *Int J Dermatol*. 2019;58(6):750-5.


## AUTHOR'S CONTRIBUTION:

**Gilmayara Alves Abreu Maciel Pereira** |  ORCID 0000-0002-0850-0427

Statistical analysis; approval of the final version of the manuscript; conception and planning of the study; elaboration and writing of the manuscript; data collection, analysis, and interpretation; effective participation in orientation of the research; intellectual participation in the propaedeutic and/or therapeutic conduct of the cases; critical review of the literature; critical revision of the manuscript.

**Diego Leonardo Bet** |  ORCID 0000-0002-7548-4797

Conception and planning of the study; data collection, analysis, and interpretation; effective participation in orientation of the research; intellectual participation in the propaedeutic and/or therapeutic conduct of the cases; critical revision of the manuscript.

**Maria Victoria Suarez Restrepo** |  ORCID 0000-0002-2614-6011

Statistical analysis; conception and planning of the study; elaboration and writing of the manuscript; data collection, analysis, and interpretation; effective participation in orientation of the research; intellectual participation in the propaedeutic and/or therapeutic conduct of the cases; critical revision of the manuscript.

**Vanessa Barreto Rocha** |  ORCID 0000-0001-6795-398X

Approval of the final version of the manuscript; elaboration and writing of the manuscript; critical review of the literature; critical revision of the manuscript.

**Leticia Arsie Contin** |  ORCID 0000-0002-4783-9909

Approval of the final version of the manuscript; conception and planning of the study; elaboration and writing of the manuscript; data collection, analysis, and interpretation; effective participation in orientation of the research; intellectual participation in the propaedeutic and/or therapeutic conduct of the cases; critical review of the literature; critical revision of the manuscript.