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Evaluation of the effectiveness of tranexamic acid in drug delivery using microneedling in the treatment of melasma

Avaliação da eficácia do ácido tranexâmico em drug delivery através de microagulhamento no tratamento do melasma

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ABSTRACT

Introduction: Melasma is a prevalent and difficult to treat skin pigmentation disorder. Tranexamic acid is a potential agent, but there are few studies on its effectiveness via the transdermal route (drug delivery).

Objective: To review the efficacy and safety profile of tranexamic acid when applied in the form of drug delivery through microneedling in the treatment of facial melasma.

Methods: This review collected data published on virtual platforms in Portuguese and English by searching through MESH/DeCS descriptors, with the terms: "melasma, tranexamic acid, drug delivery, microneedling" with AND or OR search, by title or abstract. Then, considering those most related to the topic, the full texts were read.

Result: Twenty-four articles were included.

Conclusion: Tranexamic acid in drug delivery through microneedling was not effective. However, it showed clinical safety and tolerability.

KEYWORDS: Melasma. Tranexamic acid. Drug delivery. Microneedling.

RESUMO

Introdução: O melasma é um distúrbio de pigmentação da pele prevalente e de difícil tratamento. O ácido tranexâmico é agente potencial, mas há poucos estudos sobre sua eficácia pela via transdérmica (drug delivery).

Objetivo: Revisar a eficácia e perfil de segurança do ácido tranexâmico quando aplicado na forma de drug delivery através de microagulhamento no tratamento do melasma facial.

Métodos: Esta revisão colheu dados publicados em plataformas virtuais em português e inglês por busca através de descritores MESH/DeCS, com os termos: "melasma, ácido tranexâmico, drug delivery, microagulhamento" e em inglês "melasma, tranexamic acid, drug delivery, microneedling" com busca AND ou OR, pelo título ou resumo. Em seguida, considerando-se os de maior relação ao tema, foi lida a íntegra dos textos.

Resultado: Foram incluídos 24 artigos.

Conclusão: O ácido tranexâmico em drug delivery por meio de microagulhamento não se mostrou eficaz. No entanto, apresentou segurança clínica e tolerabilidade.

PALAVRAS-CHAVE: Melasma. Ácido tranexâmico. Drug delivery. Microagulhamento.

Microneedling procedure with homogeneous erythema endpoint

Central Message

Melasma is a skin pigmentation disorder characterized by brownish spots, most commonly on the face. It is more common in women, with a higher phototype, of childbearing age. Due to its predominantly facial involvement, high prevalence and high rate of recurrence to treatments, they have an important impact on quality of life. This review seeks to update the results of treatment of this disturbing condition.

Perspective

The microneedling technique uses a device formed by 1 roller of microneedles that are applied to the skin in back and forth movements, with the aim of generating multiple micropunctures capable of crossing the stratum corneum reaching the dermis. When substances are applied to these micropunctures, their absorption is facilitated through the cutaneous pertuites generated. This transdermal delivery of substances is called drug delivery and is often used in the treatment and management of facial melasma.

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INTRODUCTION

Melasma is a skin pigmentation disorder characterized by brownish spots, most commonly on the face. It is more common in women, with a higher phototype, of childbearing age. Due to its predominantly facial involvement, high prevalence and high rate of recurrence to treatments, they have an important impact on quality of life.[1,2] Some indices have already been validated to measure this impact, such as the MelasQol (Melasma Quality of Life)3,4, and also to assess its clinical severity, such as the MASI (Melasma Area and Severity Index).[5]

The exact pathophysiology of melasma is not yet known, but genetic and triggering factors (ultraviolet radiation, pregnancy, use of hormonal therapies, photosensitizing medications, inflammatory stimuli and stressful events) are already well described.[1] Triggers act by stimulating the plasmin pathway. There is stimulation of phospholipase precursor factors A2, release of fibroblast growth factors, arachidonic acid synthesis, release of prostaglandins that lead to melanogenesis and angiogenesis.[2,6,7]

One of the medications that have the effect of inhibiting the plasmin pathway is tranexamic acid (TA).[2,6,7] It acts by blocking the melanogenesis and angiogenesis pathway, reducing hyperpigmentation.[2,6] TA can be administered by several routes: oral, topical, microinjections or microneedling.[8] This technique consists of a system of microneedles applied to the skin, generating multiple loops that facilitate the transdermal absorption of the substances.[9] This transdermal delivery is called drug delivery.[10] In addition to being a technique that promotes drug delivery, microneedling seems to contribute in isolation to the treatment of cutaneous hyperpigmentation by mechanisms not yet known.[11]

Thus, the objective of this review in the treatment of facial melasma was to review the efficacy of tranexamic acid when applied in the form of drug delivery through microneedling, verifying the safety and tolerability profile of this acid when applied with this method.

METHOD

This review collected data published on virtual platforms in Portuguese and English. The platforms used were SciELO, Google Scholar, Pubmed, and Scopus. Initially, there was a search for MESH/DeCS descriptors, with the terms in Portuguese: "melasma, tranexamic acid, drug delivery, microneedling" and in English "melasma, tranexamic acid, drug delivery, microneedling" with AND or OR search, by title or abstract. Then, considering those with the greatest relation to the theme, the full texts were read and 24 articles were included.

DISCUSSION

Melasma

Melasma is characterized by irregular, brownish macules, symmetrically distributed in photoexposed areas, most commonly on the face. It is more common in women, with a higher phototype (III-IV) and of childbearing age. Prevalence may vary according to ethnicity, phototypes, and aggravating factors. In Brazil, it has a high prevalence due to the great ethnic miscegenation and exposure to the tropical climate, and it is estimated that 15-35% of adult women are affected by it (Figure 1).

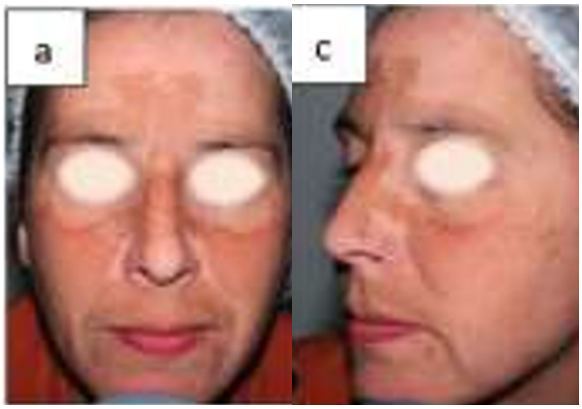


FIGURE 1 — Face with melasma: A) frontonasal; B) nasomalar

Impact of melasma on quality of life

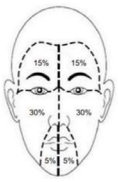
The aesthetic alteration caused by melasma influences self-image and often leads to feelings of frustration and embarrassment, and can even affect interpersonal relationships.[3] Careful evaluation of the impact is necessary, since clinical severity is not always proportional to the emotional reaction.[12] This relevant influence on psychological, emotional and social aspects justifies efforts to develop and investigate therapies that can really be effective and contribute to this scenario.

Quality of Life Index

It can be measured by the MelasQol (Melasma Quality of Life) tool, which evaluates through 10 questions, scored from 1 to 7, the patients' perception of this interference.[3,4]

Area index and clinical severity

Clinical severity can be measured by the MASI index, which records the extent of the area involved, the degree of intensity of hyperpigmentation, and the degree of homogeneity of hyperpigmentation according to the region (frontal, right malar, left malar, and chin). For clinical study purposes, this index can be adapted to an individualized measurement of the affected hemiface: the hemi-MASI. It allows comparative analyses between hemifaces to be performed (Figure 2).[13]



Fronte 0,15 × (D + H) × A + Malar 0,30 × (D + H) × A + Mento 0,05 × (D + H) × A

A (Percentage of area involved)	D (Intensity of hyperpigmentation)	H (Degree of homogeneity of hyperpigmentation)
0 = 0% 1 = 1% a 9% 2 = 10% a 29% 3 = 30% a 49% 4 = 50% a 69% 5 = 70% a 89% 6 = 90% a 100%	0 = absent 1 = light 2 = moderate 3 = marked 4 = maximum	0 = absent 1 = light 2 = moderate 3 = marked 4 = maximum

Source: Adapted from Pazyar et al. (2019)14

FIGURE 2 — Hemi-MASI calculus

Pathophysiology

The exact pathophysiology of melasma is not yet known. However, some triggering factors are already well described, such as ultraviolet radiation, pregnancy, use of hormonal therapies, photosensitizing medications, inflammatory stimuli and stressful events. Genetic factors are also involved, also evidenced by the high prevalence of associated family history.[1]

These triggers act by stimulating keratinocytes to produce plasminogen-activating factors which, in turn, transform plasminogen into plasmin. Through the activation of phospholipase A2 precursors, it stimulates fibroblast growth factors and arachidonic acid. The growth factors of fibroblasts and prostaglandins, generated by the stimulation of arachidonic acid, stimulate melanogenesis. In addition, plasmin is also believed to act in stimulating angiogenesis by converting angiogenic factors such as VEGF (vascular endothelial growth factor) into active forms.[2,6,7] The role of angiogenesis has been studied and has been shown to increase vascularization and angiogenic factors such as VEGF in the affected skin.[15] It is debated whether this increase is secondary to photodamage, already evidenced in skin with melasma16, or whether there is a direct involvement of angiogenesis in melanogenesis. Another factor that may contribute to angiogenesis is the secretion of angiogenic factors by mast cell cells, which are increased in areas of melasma (Figure 3).[17]

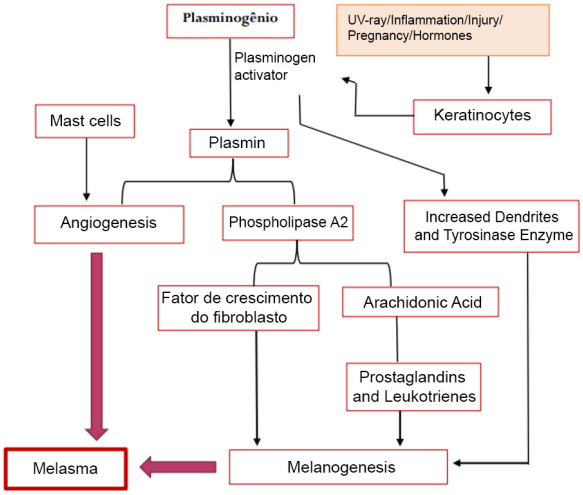


FIGURE 3 — Pathophysiology of melasma

Treatment

Tranexamic acid

One of the medications that has the effect of inhibiting the plasmin pathway is AT, a synthetic, hydrophilic substance derived from the amino acid lysine.[2,6,7] Classically, it is used as a hemostatic agent in cases of heavy menstrual bleeding and in the prophylaxis of hemorrhage in tooth extractions in patients with hemophilia. For this purpose, however, it is used orally and in a daily dose 6 times higher than that recommended for its use in the treatment of melasma.[2] AT acts by blocking the conversion of plasminogen to plasmin by inhibiting the plasminogen activator. Without plasmin, there is no stimulation of angiogenesis or activation of melanocytes by the action of phospholipase A2 and arachidonic acid. In addition, with the inhibition of the plasminogen activator, there is direct blockade in the melanocytic dendrites and production of the enzyme tyrosinase.[6] Therefore, it is through the blockade of the plasminogen activator that AT acts on melanogenesis and angiogenesis, reducing hyperpigmentation.[2,6In] addition to its action on plasmin inhibition, AT also acts on the reduction of mast cell cells, also contributing to the reduction of angiogenesis by this route (Figure 4).[17] TA has been widely studied in its oral and topical administration, by microinjections or microneedling.[8]

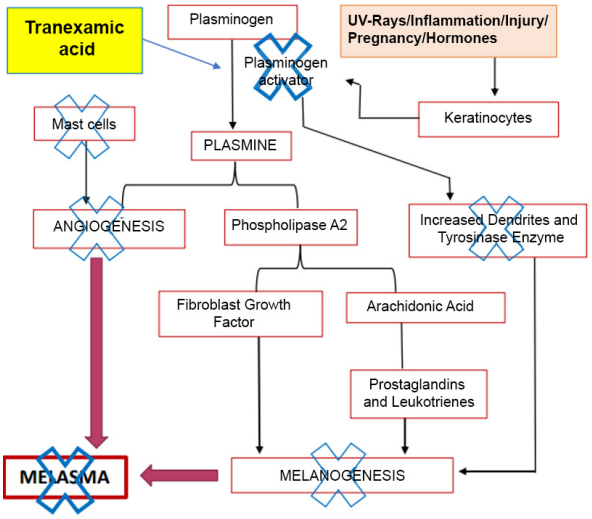


FIGURE 4 — Action of tranexamic acid on the pathophysiology of melasma

Microneedling and drug delivery

The microneedling technique uses a device formed by 1 roller of microneedles that are applied to the skin in back and forth movements, with the objective of generating multiple micropunctures capable of crossing the stratum corneum reaching the dermis (Figure 5).[9] When substances are applied to these micropunctures, their absorption is facilitated through the cutaneous pertuites generated. This transdermal delivery of substances is called drug deliver.[10,18]

FIGURE 5 — A) Microneedling procedure with homogeneous erythema endpoint; B) microneedle roller used in the technique.

Microneedling itself, in isolation, despite its usefulness as a drug delivery facilitator, can contribute to the treatment of cutaneous hyperpigmentation by mechanisms not yet known.[11] The mechanism of action of this technique is not completely known. Pilot study by Cassiano et al. (2019)19 evaluated the histological changes after 7 days of microneedling in 10 patients with melasma and observed a significant reduction in melanin, pendular melanocytes, and damage to the basement membrane. In addition, mild epidermal hyperplasia, subepidermal deposition of extracellular substances, proliferation of fibroblasts and ki67-labeled keratinocytes, representative of cell proliferation, were also observed.

Other studies have also been carried out to evaluate the action of depigmenting agents by drug delivery through microneedling. Fabbrocini et al. (2011)20 compared the efficacy of depigmenting agents alone (alpha-Sophora and Rucinol) or under drug delivery by microneedling in 20 patients in split-face format, performed with the depigmenting agent in drug delivery on the right hemiface and only the depigmenting agent on the left hemiface. This study showed a greater reduction in hyperpigmentation on the side treated with microneedling. However, it is not clear whether the improvement on the side associated with microneedling was due to increased permeation of the depigmenting active ingredient and/or to the whitening action of the microneedling itself. The same issue arises with the global improvement of cutaneous hyperpigmentation with vitamin C by drug delivery through microneedling in the study by Ismail et al. (2019)21. In this study, 30 patients received 6 sessions with an interval of 2 weeks and showed a significant reduction in the MASI at the end of the treatment. Xu et al. (2017)22 compared the efficacy of topical tranexamic acid in one hemiface and drug delivery by microneedling in the other, also obtaining a greater reduction in hyperpigmentation in the hemiface treated with microneedling. In turn, Menon et al. (2019)23 comparing microneedling with AT vs vitamin C in drug delivery found no differences between these two treatments, reinforcing the idea that microneedling itself may be responsible for the results.

Clinical improvement has a relevant positive impact on quality of life (23% reduction in mean MelasQol). Cestari et al. (2006)3 showed a significant relationship between clinical severity (calculated using the MASI) and quality of life (measured by MelasQol). However, Jusuf, Putra and Mahdalena (2019)12 did not obtain the same results. There was no statistically significant relationship, demonstrating that the most clinically severe condition is not always the one that will generate the greatest impact on quality of life, and they conclude that there is a need for a psychological evaluation so that the social impact is not underestimated.

Arida DKK et al.[24] in drug delivery reported that treatment by means of microneedling was not effective in the treatment of facial melasma. On both sides, with and without TA, there was improvement in melasma; however, there was no significant difference when comparing the sides with each other, suggesting that AT under drug delivery did not present additional benefit.[25]

CONCLUSION

It was verified that the application of TA by the transdermal route was safe and well tolerated. The adverse effects were mild and transient, resulting from the microneedling technique itself and not from the active ingredient used.

Authors' contributions

Conceptualization: Dâmia Kuster Kaminski Arida
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Writing (original draft): Ronaldo Mafia Cuenca
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