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EFFECTIVENESS AND SAFETY OF TRANEXAMIC ACID IN THE TREATMENT OF MELASMA: A SYSTEMATIC REVIEW

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Abstract: This systematic review confirmed the significant efficacy of tranexamic acid (TXA) in reducing pigmentation in patients with melasma, demonstrated by improvements in the severity indices of the condition, such as the Melasma Area and Severity Index (MASI) and the Melanin Index (MI). The results indicated benefits in both monotherapy and combination treatments, with noticeable clinical responses often observed in 8 to 12 weeks, regardless of the route of administration. A comparative analysis of the routes of administration revealed that oral TXA promotes a faster reduction in pigmentation indices and is indicated for moderate to severe cases, although it is associated with mild adverse effects, such as gastrointestinal symptoms. Topical application stood out for its safety and tolerability, making it a choice for mild cases or patients with systemic contraindications. Intradermal administration, on the other hand, has shown localized efficacy and is useful in refractory cases. Adverse events related to the use of TXA were generally mild and self-limiting, with a higher prevalence of skin irritation in the topical route and gastrointestinal discomfort in the oral route. The intradermal route presented an even more favorable profile. Despite the promising results, the review identified important limitations, such as methodological heterogeneity, small sample sizes and the absence of standardized protocols, which make it difficult to generalize the findings. Future clinical trials should prioritize the standardization of evaluation methods, studies with greater methodological rigour and prolonged follow-up to assess the durability of the benefits and long-term safety. The growing recognition of TXA in the management of melasma reflects its positive impact on even skin tone and patients' quality of life. The exploration of therapeutic combinations and predictive biomarkers could consolidate TXA as a first-line approach in the treatment

of melasma, especially in high-prevalence populations.

Keywords: "Tranexamic Acid," "Melasma Treatment," "Hyperpigmentation," "Safety Profile," "Efficacy"

INTRODUCTION

Melasma is an acquired pigmentation disorder that manifests itself as hyperchromic patches on the skin, especially on the face [1,2,3]. Unlike congenital conditions, it develops throughout life and has a slow progression, with the spots gradually growing in size and intensity [1,2,3]. Generally symmetrical, these lesions are characterized by dark brown, grey-brown or even grey-blue areas with ill--defined boundaries [1,2,3]. The spots usually appear in regions exposed to solar radiation, and are more frequent in the centrofacial, malar and mandibular regions [1,2,3,4].

Melasma mainly affects women and is particularly prevalent in people of reproductive age [3,4]. Its incidence is higher in people with skin phototypes IV to VI, such as those of Latin, Asian and black origin, whose skin is more predisposed to hyperpigmentation [3,4,5]. Among the most relevant risk factors are prolonged exposure to ultraviolet radiation, hormonal changes, such as those that occur during pregnancy or with the use of oral contraceptives, and genetic predisposition [3,4,5,6]. The use of certain medications and cosmetic products can also trigger or aggravate spots [3,4,5,6]. These factors make melasma a multifactorial condition, with a different impact among population groups [6].

Melasma is classified into three main types: epidermal, dermal and mixed, according to the location of the melanin in the skin, which can be determined by specific tests such as Wood's lamp or skin biopsy [6]. Studies show that affected skin shows increased vascularization and melanin production, phenomena often associated with changes in cell regulation and chronic exposure to the sun [6,7]. In addition, the presence of angiogenic factors, which stimulate the formation of new blood vessels in the epidermis, can also contribute to the development and persistence of spots [6,7]. This complex interaction between pigmentation and vascularization makes the treatment of melasma a clinical challenge [6,7].

In addition to the physical changes, melasma can have a significant impact on the self-esteem and quality of life of those affected [6,7,8]. The visibility of the spots, especially on the face, often leads to feelings of embarrassment and insecurity, affecting social interaction and, in some cases, contributing to anxiety or depression [6,7,8]. The chronic nature and frequent recurrences of the condition also aggravate the emotional impact, as many people find it difficult to find effective and long-lasting treatments [6,7,8]. Thus, the management of melasma goes beyond cosmetic correction, involving attention to psychological aspects [6,7,8].

The treatment of melasma often combines topical strategies, cosmetic procedures and preventive measures [8]. Among the most commonly used topical agents are hydroquinone, tretinoin and corticosteroids, often associated in combination formulas to maximize the whitening effect [8]. Other substances, such as kojic acid and azelaic acid, are effective and milder alternatives, especially suitable for patients with sensitive skin [8,9]. Cosmetic procedures, such as superficial chemical peels, lasers and intense pulsed light (IPL), also play an important role, promoting the removal of superficial layers of pigmented skin and even out skin tone [8,9]. However, these procedures require caution, as irritation can aggravate hyperpigmentation [9].

Tranexamic acid (TXA), originally developed to control bleeding, has gained prominence as an innovative approach to treating melasma [10,11,12]. It acts by inhibiting the

conversion of plasminogen into plasmin, reducing inflammation and the stimulation of melanocytes, the cells responsible for melanin production [10,11,12]. TXA thus minimizes the inflammatory activity and hyperpigmentation characteristic of the disease [10,11,12]. It can be applied topically, with creams and gels, or systemically, in tablet form, depending on clinical need [10,11,12]. Studies show that the combined use of TXA with other treatments can speed up improvement and prevent relapses [12].

Tranexamic acid is most effective when integrated into a comprehensive therapeutic plan that includes topical lightening agents, rigorous sun protection and, if indicated, aesthetic procedures [12]. Photoprotection with broad-spectrum sunscreens is crucial to prevent the progression of melasma and ensure better results [12,13]. Treatment should be personalized, taking into account factors such as skin phototype, extent of lesions and clinical history [12,13]. Supervision by a dermatologist is indispensable to monitor efficacy, adjust interventions and minimize potential adverse effects, ensuring safe and effective management [12,13].

OBJECTIVES

To evaluate the efficacy, safety and clinical impact of tranexamic acid (TXA) in the treatment of melasma, focusing on the different routes of administration (oral, topical and intradermal), their therapeutic implications and the challenges associated with the practical application of the findings [12,13]. The review also aims to identify gaps in the literature, proposing directions for future research, including long-term studies and standardization of evaluation methods [13].

METHODS

This work consists of an integrative review, a methodological approach that allows us to synthesize available evidence from different studies, promoting a comprehensive view of the subject under investigation [14]. The integrative review is essential for consolidating knowledge about the use of tranexamic acid in the treatment of melasma, assessing its efficacy, safety and role in the management of this dermatological condition [14]. By gathering recent, high-quality data, this methodology helps support evidence-based clinical decisions and identifies gaps in knowledge that can direct future research [14,15].

The survey of studies was carried out in the PUBMED, VHL and MEDLINE databases, covering articles published between 2018 and 2023, exclusively in English [15]. The keywords used included: *"Tranexamic Acid"*, *"Melasma Treatment"*, *"Hyperpigmentation"*, *"Safety Profile"* and *"Effectiveness"* [15]. To ensure the accuracy and relevance of the results, the search used Boolean operators and filters for date, language and type of publication [15].

The article selection process followed three rigorous stages. In the first stage, 835 articles were identified using a combination of descriptors [15,16]. Additional filters were applied to exclude studies outside the period of analysis, non-peer-reviewed publications and articles in languages other than English [15,16]. In the second stage, an initial screening was carried out based on titles and abstracts, excluding duplicate studies, narrative reviews, experimental animal trials, dissertations, theses and articles irrelevant to the topic. As a result, 217 studies were selected for full reading [15].

In the third stage, the selected articles were fully evaluated, applying additional exclusion criteria [15]. Publications with insufficient or inconsistent data, studies without clear methodology or which did not present relevant

results on the efficacy or safety of tranexamic acid in the treatment of Melasma [15] were eliminated. After careful analysis, 41 studies were considered eligible and included in the final analysis, ensuring that the integrative review brought together the most relevant and robust evidence to support conclusions on the subject [15].

RESULTS

The studies analyzed in this integrative review showed that tranexamic acid (TXA) has a significant impact on reducing the *Melasma Area and Severity Index* (MASI) and other indices used to assess pigmentation, such as the *Melanin Index* (MI) [16,17,18,19]. Patients treated with TXA often present statistically significant decreases in these scores, indicating relevant clinical improvement [16,17,18,19]. The positive effect of TXA has been observed both in monotherapy and in combination with other treatments, such as topical whitening agents [16,17,18,19]. The results suggest that TXA reduces the intensity of spots and evens out skin tone, with noticeable benefits after an average period of 8 to 12 weeks of treatment, depending on the route of administration and the initial severity of Melasma [16,17,18,19].

Comparing the different routes of administration, oral use of TXA has been associated with a faster and more consistent reduction in pigmentation indices, while topical application has a lower incidence of adverse effects and is more suitable for patients with contraindications to systemic use [16,17,18,19]. Intradermal administration, on the other hand, has shown promising results in refractory cases, especially when combined with other treatments [17,18,19]. Despite these differences, all methods require a prolonged period of use to achieve significant results, reinforcing the importance of dermatological follow-up and adherence to treatment for the effective management of Melasma [16,17,18,19].

The studies included in this review were of varying methodological quality, with limitations that should be considered when interpreting the results [19]. Among the main limitations are the small sample sizes in many of the studies, making it difficult to generalize the findings to larger populations [19]. In addition, the lack of standardization in the methods used to assess efficacy, such as the different indices and clinical criteria used, compromises direct comparison between studies [19]. The short follow-up period in most of the studies also limits the assessment of the long-term effects of tranexamic acid (TXA), especially in relation to the maintenance of the results obtained and the safety of the treatment. Despite these restrictions, the findings are relevant to populations with a high prevalence of melasma, such as those with phototypes III to V and in regions with high sun exposure, suggesting that TXA may be a promising alternative for managing the condition in a variety of contexts [19,20,21,22,23].

In order to advance knowledge about the use of TXA in the treatment of melasma, there is an urgent need for additional studies with more robust methodological designs [19,20,21,22,23]. Clinical trials with a larger number of participants, longer follow-up periods and standardization of evaluation indices would be essential to confirm the preliminary results and provide greater reliability to the available evidence [19,20,21,22,23]. Furthermore, future research could explore the potential of TXA in combination with other therapies, such as whitening agents or laser procedures, to assess therapeutic synergy and its effectiveness in refractory cases [22,23]. Another promising area is the investigation of biomarkers that can predict the individual response to TXA, allowing for a more personalized and effective treatment [23]. These initiatives could consolidate TXA as a widely validated therapeutic option for the management of Melasma [24].

Research into the use of biomarkers in the treatment of melasma with tranexamic acid (TXA) is a promising area that seeks to personalize and optimize therapeutic approaches for this dermatological condition [24,25]. Biomarkers, such as genetic variations, protein levels or specific metabolites, can help predict how each individual will respond to treatment, allowing for more personalized medicine [25,26,27,28]. This is particularly important because not all patients show the same efficacy when using TXA, and identifying these indicators can direct treatment towards those most likely to succeed, avoiding unnecessary interventions and minimizing the risks of adverse effects [25,26,27,28,29].

Furthermore, the identification of biomarkers brings benefits that go beyond the personalization of treatment [25,26,27,28,29]. It can guide the creation of new, more targeted and effective therapies, expanding the options available for managing Melasma [28,29]. It also enables more detailed monitoring of clinical progress, with precise adjustments to the dosage and frequency of medication [30,31]. In the long term, this approach may even contribute to the prevention of melasma in people with a greater predisposition, marking a significant advance in dermatology [30,31]. By aligning treatment, monitoring and innovation, the use of biomarkers has the potential to transform the way melasma is understood and treated [31,32].

DISCUSSION

The studies analyzed in this review confirmed the significant efficacy of tranexamic acid (TXA) in reducing pigmentation in patients with melasma [31,32,33]. This effect was demonstrated by a statistically significant decrease in the indices used to measure the severity of the condition, such as the Melasma Area and Severity Index (MASI) and the Melanin Index (MI) [31,32,33]. TXA has shown benefits both in monotherapy and as an adjuvant in combined treatments, reinforcing its potential as a versatile therapeutic tool. Over periods of 8 to 12 weeks, patients often reported noticeable clinical improvement, regardless of the route of administration [33,34].

INTERPRETATION OF RESULTS

The results of the review show significant differences between the routes of administration of tranexamic acid (TXA) in the treatment of melasma, with direct implications for the choice of therapy [33,34,35,36]. The oral route stood out for its consistent efficacy, providing a faster reduction in pigmentation indices, such as the Melasma Area and Severity Index (MASI) [35,36]. This makes it an attractive option for moderate to severe cases, especially in patients looking for faster results [35,36,37]. However, the risk of adverse effects, although generally mild and self-limiting, such as gastrointestinal symptoms, may limit its application in individuals with contraindications or greater sensitivity to systemic treatments [35,36,37].

On the other hand, topical application has shown safety-related advantages, with a superior tolerability profile, and is particularly indicated for mild cases or patients who cannot use the systemic route [35,36,37]. Although the results may be less immediate, topical use allows for prolonged and safe management of the condition [35,36,37]. Intradermal administration, although less explored, has proved to be a valuable alternative in refractory cases, standing out for its localized efficacy and potential for therapeutic combinations [36,37]. With an acceptable safety profile and good acceptance by patients, this approach offers new perspectives, especially for individuals who do not respond adequately to more conventional options [36,37].

SECURITY

The adverse events associated with the use of tranexamic acid (TXA) were considered to be mostly mild and self-limiting, reinforcing its safety profile when administered under adequate medical supervision [36,37,38]. In topical application, the most frequent reactions included mild skin irritation, while oral administration was associated with gastrointestinal discomfort, such as nausea and abdominal pain [36,37,38]. The intradermal route presented an even more favorable profile, with a low incidence of significant side effects. Despite the overall safety profile, continuous monitoring of patients remains essential in order to identify possible complications early on and make adjustments to therapy when necessary [36,37,38].

IMPACT AND RECOGNITION

The growing recognition of TXA in the management of melasma reflects the combination of its clinical efficacy with a largely favorable safety profile [36,37,38]. This is especially relevant in the context of treatments for high phototypes, which often present specific challenges due to a greater tendency towards post-inflammatory hyperpigmentation [37,38]. In addition, TXA has shown a considerable impact on skin tone evenness and overall aesthetic improvement, critical factors for therapeutic success and patient satisfaction [37,38]. As future studies expand our understanding of its mechanisms of action and administration strategies, TXA has the potential to become an essential component in the therapeutic arsenal against melasma [38].

LIMITATIONS OF THE REVIEW AND FUTURE PERSPECTIVES

Although the results of this review are promising, significant limitations have been identified which should be considered when interpreting the findings [38,39]. Heterogeneity in the methods used to assess efficacy and the lack of standardized therapeutic protocols make it difficult to directly compare the studies analysed [38,39]. Furthermore, the small sample sizes in many studies limit the generalizability of the results [39]. Another critical factor is the short duration of follow-up in most studies, which prevents a more robust analysis of the maintenance of long-term therapeutic benefits and the occurrence of late adverse events [39].

The lack of uniformity in evaluation criteria and therapeutic protocols presents challenges in the practical application of the results, especially when treating refractory or long-standing cases [39,40,41]. The lack of data on long-term safety also raises concerns, considering that melasma is a chronic condition that requires continuous interventions [39,40,41]. These factors reinforce the need for caution when implementing the approaches reviewed, as well as highlighting the importance of rigorous and individualized clinical follow-up [39,40,41]

Larger clinical trials, with greater methodological rigor, are essential to validate the findings of this review and advance the use of tranexamic acid (TXA) as a therapeutic option [39,40,41]. Future studies should prioritize the standardization of assessment methods, such as the universal adoption of established indices like the *Melasma Area and Severity Index* (MASI) and the *Melanin Index* (MI), to facilitate the comparability of results [39,40,41]. Research into therapeutic combinations, such as TXA associated with bleaching agents or laser-based technologies, has the potential to offer more effective solutions for refractory cases [39,40,41].

In addition, the identification of predictive biomarkers may allow for the personalization of treatment, maximizing the benefits and minimizing the risks of adverse effects [39,40,41]. Progress in the use of TXA could redefine the management of melasma, making it more effective and accessible, especially in high-prevalence populations [39,40,41]. The implementation of studies with prolonged follow-up is also key to assessing the safety and stability of results over time, reinforcing confidence in the benefits of TXA [39,40,41]. By combining robust science, therapeutic innovation and personalized strategies, TXA has the potential to consolidate itself as a first--line approach to treating this dermatological condition, which profoundly impacts patients' quality of life [39,40,41].

It is important to note that the risk-benefit assessment of TXA must be carried out individually, taking into account the clinical characteristics and medical history of each patient [40,41]. The choice of route of administration and the duration of treatment should be adjusted according to the response to treatment and the tolerance observed [40,41]. In addition, the association of TXA with other therapies for melasma can reduce the need for higher doses or prolonged periods of use, contributing to the overall safety of the therapeutic protocol [41].

CONCLUSION

Therefore, according to the studies analyzed, tranexamic acid (TXA) corroborated the reduction of melasma, as proven by indices such as (MASI) and (MI). This positive effect of (TXA) can be observed in both monotherapies and polytherapies.

Regarding the routes of administration, the oral use of (TXA) had a faster reduction, making it ideal for moderate and severe cases. Topical application had fewer adverse effects and is indicated for patients with contraindications.

Intradermal administration has shown promising results for refractory cases, demonstrating greater efficacy when combined with other treatment methods. However, all methods require a prolonged period of use in addition to dermatological medical monitoring.

Despite the limitations of the study, such as the size of the sample, the lack of standardization in the evaluation methods and the short follow-up period, the information collected is of great relevance to the population with a high rate of melasma, which places the use of (TXA) as a promising alternative for controlling hyperpigmentation in various contexts.

In order to ensure scientific progress on the subject, there is a need for clinical trials with a larger number of participants, prolonged follow-up , standardization of evaluation indices and the use of biomarkers that tend to optimize the therapeutic approach.

Regarding the safety of (TXA), most of its side effects were considered to be mild and self-limiting, which reinforces its efficacy and safety when applied under medical supervision. In topical application, reactions include mild skin irritation, in the oral route symptoms associated with gastrointestinal discomfort and in the intradermal route it presented low incidences of side effects.

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