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Use of tranexamic acid in melasma

Tranexamic acid (TA) is an old drug used for a long time to treat or prevent excessive blood loss. In the beginning of the 1950s it was discovered that the amino acid lysine was able to inhibit activation of plasminogen, but the effect was too weak to be a candidate for the treatment of fibrinolytic haemorrhagic conditions. The first mention of TA in dermatology was in 1979 in actinic prurigo, with good results. Later it was demonstrated in vitro that TA was able to block melanogenesis. During the 2010's more and more trials were published, assessing its efficacy in melasma, but also in erythrotelangiectasic rosacea.

First, systemic TA was prescribed, but soon, because of the rare but severe complications susceptible of occurring, topical way was tested, giving similar results without risk of side effects. The particular interest of TA in the management of melasma is due to that it displays an activity at various levels.

First, TA was shown to downregulate the activity of mast cells and consequently the release of histamine. Following the review of the currently available literature concerning the use of TA in melasma, it appears that this active ingredient permits achieving a good efficacy in this indication where there is no satisfactory therapy, with minor side effects. There are mainly three modalities of treatment of melasma with TA: oral administration and intradermal and topical applications. From the literature reviewed, it appears that the best results can be achieved by intradermal administration of TA (4 mg/l monthly) or topical 3 % TA (2/day).

At this stage, the limitations of the currently available data are double: first, most of studies are concerning Asian skin, and secondly there is a lack of a large scale comparative study encompassing these three different ways of administration, which could confirm (or not) our analysis of currently published data.

Key words

Tranexamic acid, melasma, melanogenesis, skin.

Tranexamic acid (TA) is an old drug used for a long time to treat or prevent excessive blood loss. The first mention of TA in dermatology was in 1979 in actinic prurigo, with good results.

Later it was demonstrated in vitro that TA was able to block melanogenesis. During the 2010's more and more trials were published, assessing its efficacy in melasma, but also in erythrotelangiectasic rosacea. First, systemic TA was prescribed, but soon, because of the rare but severe complications susceptible of occurring, topical way was tested, giving similar results without risk of side effects. In this review we shall bring a summary of published clinical trials using systemic or topical TA in melasma and intend to compare the efficacy and safety of both regimens. Mechanism of action of TA will also be investigated.

INTRODUCTION

In the beginning of the 1950s it was discovered that the amino acid lysine was able to inhibit activation of plasminogen, but the effect was too weak to be a candidate for the treatment of fibrinolytic haemorrhagic conditions [1]. In 1962 such a substance was found: 4-aminomethyl-cyclohexane-carbonic acid (AMCHA). This compound contains two stereoisomers and Okamoto et al. [2] revealed that only the trans-form was antifibrinolytic (trans-4 aminomethylcyclohexanecarboxylic acid), and so trans-AMCHA also named tranexamic acid (TA) was born. Used since then to treat or prevent excessive blood loss from major trauma, postpartum bleeding, surgery, tooth removal, nosebleeds, and heavy menstruation, TA is presented under oral form (usually tablet), but also as intravenous injection. TA exerts its anti-haemorrhagic effect by reversibly blocking lysine binding sites on plasminogen molecule, thus inhibiting plasminogen activator (PA) from converting plasminogen to plasmin.

The first mention of TA in dermatology was in 1979. López-Gonzalez et al. reported a very good result by using oral TA in actinic prurigo [3]. Much

later TA was again under study in dermatology in 1998, when Maeda et al. demonstrated in vitro that TA was capable to block melanogenesis [3].

MELASMA AND ITS PATHOGENESIS

Melasma is a common cause of facial hyperpigmentation affecting millions of individuals worldwide. Exposure to sunlight, oral contraceptives and pregnancy may exacerbate melasma.

Treatment includes topical depigmenting agents, chemical peels, laser and energy devices.

Genetic factors, UV exposure, and a role of female sex hormones were classically described as causes of melasma. However, the accumulated knowledge to date has revealed that melasma was not merely an hyperpigmentary disorder, but more likely a specific entity, involving many more cells than melanocytes alone. Transcriptional analysis showed that various dermal components are involved in melasma. For instance, the Wnt signalling modulators secreted from fibroblasts are upregulated in lesional melasma skin compared with perilesional skin [4]. The expression of Wnt inhibitory factor-1 (WIF-1) gene, expressed by skin keratinocytes and fibroblasts, was shown to be significantly reduced in the hyperpigmented skin from melasma patients, but not in healthy controls, stimulating melanogenesis and melanosome transfer through the upregulation of both canonical and non-canonical Wnt signalling pathway [5]. Periodic acid-Schiff stain and anti-collagen type IV showed damage on the basal membrane in 95.5 and 83%, respectively, in melasma lesions [6]. Thus, disrupted basal membrane can promote the descent of melanocytes and melanin into the dermis, which would appear as free melanin in the dermis. The number of blood vessels, vessel size and vessel density are greater in lesional melasma skin than in perilesional skin [7]. In the same work, it was also assessed that the expression of Vascular Endothelial Growth Factor (VEGF) was increased in melasma, making VEGF a major angiogenic factor for altered vessels in melasma. On the other hand, Endothelin-1 (ET-1) released from endothelial cells stimulates the pigmentation through endothelin receptor B activation at the surface of the melanocytes [8]. An increase in the number of mast cells has been observed more frequently in lesional melasma skin than in perilesional skin [6].

A release of histamine from mast cells in response to UV irradiation has been demonstrated to stimulate melanogenesis, which is mediated by H_2 receptors via protein kinase A activation [9]. In summary, further to melanocytes, in melasma various cell lines are involved: keratinocytes, fibroblasts, endothelial cells and mast cells, whilst the basal membrane is disrupted. This makes melasma a specific entity, different from any other hyperpigmentary disorder.

MECHANISM OF ACTION OF TA IN MELASMA

The particular interest of TA in the management of melasma is due to that it displays an activity at various levels. First, TA was shown to downregulate the activity of mast cells and consequently the release of histamine [10, 11]. TA also directly inhibits melanogenesis through suppressing the expression of prohormone convertase (PC2) and α-melanocyte stimulating hormone (α-MSH) [12]. On the other hand, TA reduces the number of blood vessels in dermis, and inhibits neovascularization induced by basic fibroblast growth factor [13, 14]. Finally, TA reduces VEGF levels by downregulating the activity of mast cells [15].

Figure summarizes the multifactorial mechanism of action of tranexamic acid on melasma.

Use of injections of TA in the treatment of melasma

Amazingly, the first two reports of use of TA for the treatment of melasma [16, 17] were with intradermal injections; in the second one [17] the results of this protocol were compared with 3% topical TA 2 bid. In total, seven studies [16, 22] were published using injectable TA for the treatment of melasma; they are listed in Table 1.

Analysis of results

The studies include 485 patients in total. There is a perfect homogeneity in the criteria of evaluation (MASI in all studies). There is also a good homogeneity in the protocol (4 mg/ml monthly except in Lee et al. [16] and Steiner et al. [17] where the application is on a weekly base.

Based on the five studies [18—22] in which the protocol of application is on a monthly base, the improvement of melasma is ranging between 35.7 and 80.7% and taking into account the number of patients in each study, the average improvement of melasma reaches 64.9%.

Weekly application of 4 mg/ml [16, 17] appears not giving better results than monthly application, all the contrary.

This protocol combined with one daily application of HQ 4% is giving better results than the protocol alone [21]. In comparative studies, the protocol brings a similar or even better improvement to melasma than oral TA 500 mg/day [19, 22] or topical application of HQ 2% once per day [20].

Side effects

Reported side effects along these studies are summarized in Table 2. Globally, there were no side

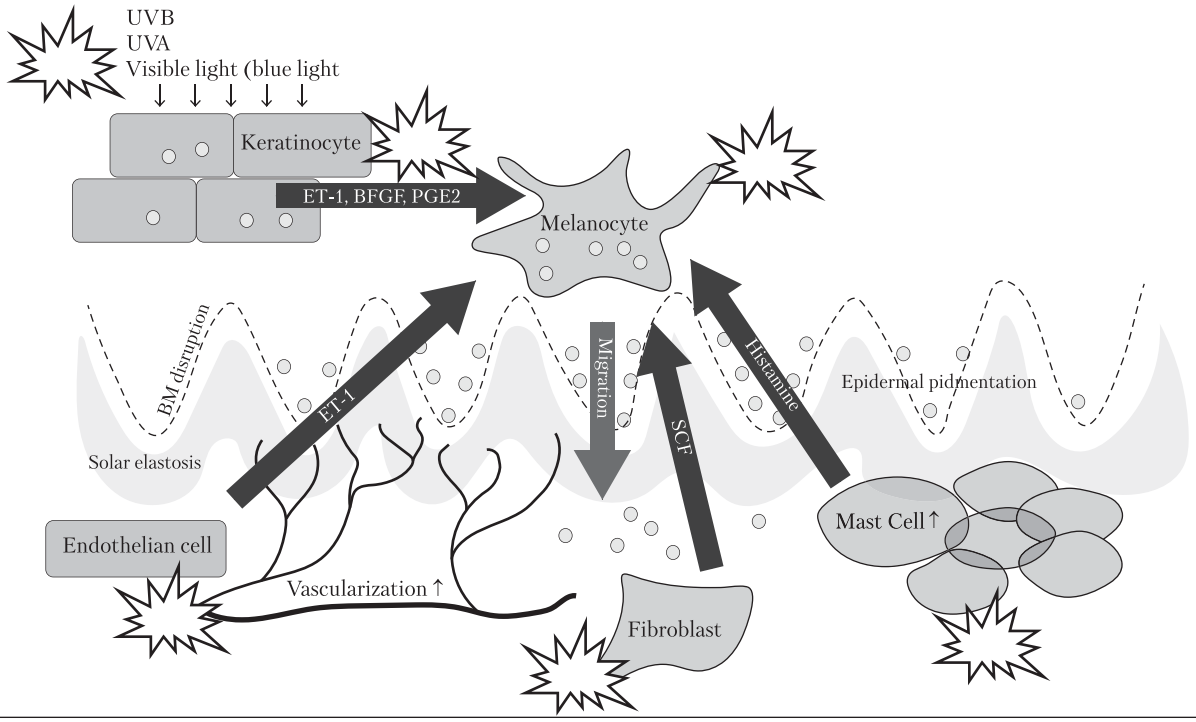

Figure. **Mechanism of action of tranexamic acid on melasma**

Table 1. **Published studies with use of intradermal TA in melasma**

Authors/year	Patients (n)	Treatment	Results (%)
Lee, 2005 [16]	100	4 mg/ml weekly — 3 months	MASI: 42.7
Steiner, 2009 [17]	9	4 mg/ml weekly — 3 months	MASI: 36.0
Budamakuntla, 2013 [18]	30	4 mg/ml monthly — 3 months	MASI: 35.7
Sharma, 2017 [19]	100	4 mg/ml monthly *vs.* 500 mg/day — 3 months	MASI 1: 77.8 MASI 2: 79
Saki, 2017 [20]	37	4 mg/ml *vs.* HQ 2 % 1/day — 3 months	MASI 1: 80.7 MASI 2: 65
Tehranchinia, 2018 [21]	55	4 mg/ml monthly *vs.* 4 mg/ml + HQ 4 % 1/day — 3 months	MASI 1: 43.8 MASI 2: 60.1
Khurana, 2019 [22]	64	4 mg/ml monthly *vs.* 500 mg/day — 3 months	MASI 1: 57.5 MASI 2: 43.5

Table 2. **Summary of side effects observed when using injectable TA in the treatment of melasma**

Authors/year	Treatment	Observed side effects
Lee, 2005 [16]	4 mg/ml weekly — 3 months	No side effect was observed
Steiner, 2009 [17]	4 mg/ml weekly — 3 months	Minimal, well-tolerated side effects
Budamakuntla, 2013 [18]	4 mg/ml monthly — 3 months	No major side effect apart from mild discomfort, burning sensation, and erythema were observed
Sharma, 2017 [19]	4 mg/ml monthly *vs.* 500 mg/day —3 months	Injection site pain, which did not warrant discontinuation of treatment
Saki, 2017 [20]	4 mg/ml *vs.* HQ 2 % 1/day —3 months	Not mentioned
Tehranchinia, 2018 [21]	4 mg/ml monthly *vs.* 4mg/ml + + HQ 4 % 1/day — 3 months	Pruritus at the site of injection was noted in a few patients
Khurana, 2019 [22]	4 mg/ml monthly *vs.* 500 mg/day — 3 months	No major side effect was noted

Table 3. **Summary of published clinical trials with TA in melasma**

Author/year	Patients (n)	Treatment	Results (%)
Na, 2012 [23]	22	750 mg/day — 2 months	Melanin index 4 Erythema index 6.2 Epidermal pig. index 19
Wu, 2012 [24]	74	500 mg/day — 6 months	Excellent 10.8 Good 54 Fair 31.1 Poor 4.1
Karn, 2012 [25]	200	500 mg/day — 3 months	MASI: 29.2
Li, 2014 [26]	35	500 mg/day — 3 months	Marked improvement 68.6 Moderate improvement 31.4
Padhi, 2015 [27]	40	500 mg/day + depigmenting trio *vs.* depigmenting trio alone — 2 months	MASI 1: 54.6 MASI 2: 88
Tan, 2016 [28]	25	500 mg/day — 3 months	MASI: 69.3
Lee, 2016 [29]	561	500 mg/day — 4 months	Improvement 89.7
Del Rosario, 2018 [30]	39	500 mg/day — 3 months	MASI: 49
Colferai, 2018 [31]	37	500 mg/day — 3 months	MASI: 48.3
Zhu, 2019 [32]	72	500 mg/day — 2 months 1000 mg/day — 2 months 1500 mg/day — 2 months	MASI: 60.9 MASI: 65.7 MASI: 75-8

effects, or minimal, well-tolerated ones such as discomfort, or pain or pruritus at the site of injection which did not oblige to discontinue the treatment.

Use of oral ta in the treatment of melasma

Published clinical trials with oral TA in melasma are summarized in Table 3.

Analysis of results

The number of patients treated in the reviewed trials is quite high: 1105 patients in total.

The dose of TA taken by the subjects is quite homogenous: 500 mg/day in all studies except Na et al. [23]. In one study [27] this oral intake of TA was associated with a depigmenting trio (*vs.* depigmenting trio alone). Zhu et al. [32] performed the first dose/effect study, showing that the efficacy of oral TA in melasma appears to be dose dependent.

The criteria of evaluation are not homogenous: MASI in 6 studies and evaluation of improvement in 3 studies.

In the five trials strictly comparable [25, 28—32] the percentage of improvement of MASI is ranking between 29.2 and 69.3% with an average value, taking into account the number of patients in each trial, of 39.2%.

Reviewing the three studies [24, 26, 29] where the criteria of evaluation was the doctor's evaluation, it appears that the treatment with 500 mg daily TA appears to improve melasma in around 90% of patients.

Side effects

It appears from the available published reports (Table 4) that the tolerability of treatment is good, with a few non-severe and transient side effects (most often gastrointestinal discomfort and decreased menstruation). However, serious side effects must not be discarded when prescribing oral TA.

USE OF TOPICAL TA IN THE TREATMENT OF MELASMA

Published clinical trials with topical TA in melasma are summarized in Table 5.

Analysis of results

As regards the criteria of evaluation, all the mentioned studies are based on a unique criterion: MASI score. There is a good homogeneity in the duration of treatment: 3 months for all trials except [40]. We can observe that the investigators used different concentrations of topical TA, ranging from 2 to 5%. Interestingly, most studies are comparative studies, *vs.* HQ 2% [38], 3% HQ [39] or combined with 0.01% dexamethasone [34] or 4% HQ [35].

One study [40] is comparing 3% TA with 20% azelaic acid, both in combination with 250 mg oral

Table 4. **Side effects reported when using oral tranexamic acid in melasma**

Author/year	Treatment	Observed side effects
Na, 2012 [23]	750 mg/day — 2 months	Non mentioned
Wu, 2012 [24]	500 mg/day — 6 months	Gastrointestinal discomfort (5.4 %) Hypomenorrhea (8.1 %)
Karn, 2012 [25]	500 mg/day — 3 months	Non mentioned
Li, 2014 [26]	500 mg/day — 3 months	No serious adverse effects documented
Padhi, 2015 [27]	500 mg/day + depigmenting trio *vs.* depigmenting trio alone — 2 months	Systemic side effects including ophtalmological side effects were not observed in any patient
Tan, 2016 [28]	500 mg/day — 3 months	No side-effects, including gastro-intestinal and menstrual irregularities, were reported during the treatment
Lee, 2016 [29]	500 mg/day — 4 months	Adverse events occurred in 40 patients (7.1 %). Most were transient, but one developed deep vein thrombosis requiring prompt discontinuation
Del Rosario, 2018 [30]	500 mg/day — 3 months	No adverse events were noted
Colferai, 2018 [31]	500 mg/day — 3 months	No patient had severe side effects
Zhu, 2019 [32]	500 mg/day — 2 months 1000 mg/day — 2 months 1500 mg/day — 2 months	Side effects included mild stomach upset and decreased menstruation

Table 5. **Published studies with topical TA in melasma**

Authors/year	Patients (n)	Treatment	Results (%)
Steiner, 2009 [17]	9	3 % TA 2/day — 3 months	MASI: 36.0
Kanechorn, 2012 [33]	21	5 % TA 2/day — 3 months	MASI: 59.4
Ebrahimi, 2014 [34]	50	3 % TA *vs* 3 % HQ + 0.001 % Dexamethasone 2/day — 3 months	MASI 1: 66 MASI 2: 64.5
Banihashemi, 2015 [35]	30	5 % TA *vs.* 4 % HQ 2/day —3 months	MASI 1: 47.8 MASI 2: 46.1
Chung, 2016 [36]	13	2 % TA 2/day — 3 months	MASI: 75.4
Kim, 2016 [37]	23	2 % TA 2/day — 3 months	MASI: 33.6
Atefi, 2017 [38]	60	5 % TA *vs.* 2 % HQ 2/day — 3 months	MASI 1: 63.2 MASI 2: 64
Janney, 2019 [39]	100	5 % TA *vs.* 3 % HQ 1/day — 3 months	MASI 1: 27 MASI 2: 26.7
Malik, 2019 [40]	100	3 % TA 2/day+ TA 250 mg/day 20 % azelaic acid 2/day + TA 250 mg/day — 6 months	MASI 1: 58 MASI 2: 50

TA daily and another trial is comparing 3 % TA with TA microneedling [17].

The total number of volunteers was 397 taking all the trials together.

5 % TA was the most commonly used concentration, in 4 studies [33, 35, 38, 39].

These four studies include a total of 211 patients. The reduction of MASI was ranging between 27 and 63.2 % with an average reduction, taking into account the number of patients in each study, of 43.5 %.

5 % TA application was giving similar results as 2 % HQ [38], 3 % HQ [34] or 4 % HQ [37].

On the contrary, 5 % TA applications were giving better results than 20 % azelaic acid [36].

With 3 % TA applications, reductions in MASI were observed as ranging from 36 to 66 % [30, 37] with an average reduction, taking into account the number of patients in each study, of 56.1 % with topical application alone vs. 58 % when applied in combination with oral therapy [36].

Table 6. **Side effects reported with topical TA**

Authors/year	Treatment	Observed side effects
Steiner, 2009 [17]	3 % TA 2/day — 3 months	Minimal, well-tolerated side effects
Kanechorn, 2012 [33]	5 % TA 2/day — 3 months	Erythema was significant on the TA-applied site
Ebrahimi, 2014 [34]	3 % TA *vs* 3 % HQ + 0.001 % Dexamethasone 2/day — 3 months	Erythema, skin irritation, xerosis, and scaling were the side effects of TA. No serious complaints were seen with TA
Banihashemi, 2015 [35]	5 % TA *vs.* 4% HQ 2/day — 3 months	No serious adverse events occurred with TA
Chung, 2016 [36]	2 % TA 2/day — 3 months	No serious adverse effects were observed
Kim, 2016 [37]	2 % TA 2/day — 3 months	The topical formulation used was not an irritant, and there were no specific adverse events
Atefi, 2017 [38]	5 % TA *vs.* 2 % HQ 2/day — 3 months	No side effect was revealed
Janney, 2019 [39]	5 % TA *vs.* 3 % HQ 1/day — 3 months	Patient satisfaction score was higher in TA group in view of lesser side effects
Malik, 2019 [40]	3 % TA 2/day+ TA 250 mg/day 20 % azelaic acid 2/day + + TA 250 mg/day — 6 months	No report of side effect

Table 7. **Comparison of results of TA on melasma depending on the way of administration**

Way of administration	Results (Decrease in MASI score), %
Oral administration	
TA 500 mg/day	Mean 39.2 (29.2—69.3)
Intradermal administration	
4 mg/ml (0.4 %) monthly	Mean 64.9 (35.7—80.7)
Topical administration	
2 % TA 2/day	Mean 48.7 (33.6—75.4)
3 % TA 2/day	Mean 56.1
5 % TA 2/day	Mean 43.5 (27—63.2)

Results with 3% TA applications were giving slightly better results than those with 3% HQ + + 0.001% Dexamethasone [30].

Results with 2% TA were reported in 2 studies and ranging between 33.6% and 75.4% with a mean value of reduction of MASI taking into account both studies of 48.7%.

Comparing the results obtained with these three concentrations, the mean reduction of MASI was 48.7% with 2% TA, 56.1% with 3% TA and 43.5% with 5% TA. It appears clearly that 3% TA is the best concentration when using topical TA in the treatment of melasma.

Side effects

Globally, topical application of TA shows a very good tolerability (see Table 6).

In conclusion, this modality of treatment of melasma appears to be safe and without occurrence of side effects.

COMPARISON OF THE EFFICACY OF TA ON MELASMA ACCORDING TO THE WAY OF ADMINISTRATION

As we could observe from previous chapters, there are mainly three way of administration for TA in melasma: the oral one, the intradermal and the topical one.

Table 7 reflects a comparison between the results of treatment by each way of administration. As we can see, the best results can be achieved by intradermal administration of TA (4 mg/ml monthly) or topical 3% TA (2/day).

Conclusions

Following the review of the currently available literature concerning the use of TA in melasma, it appears that this active ingredient permits achieving a good efficacy in this indication where there is no satisfactory therapy, with minor side effects.

There are mainly three modalities of treatment of melasma with TA: oral administration and intradermal and topical applications.

From the literature reviewed, it appears that the best results can be achieved by intradermal administration of TA (4 mg/ml monthly) or topical 3% TA (2/day).

At this stage, the limitations of the currently available data are double: first, most of studies are concerning Asian skin, and secondly there is a lack of a large scale comparative study encompassing these three different ways of administration, which could confirm (or not) our analysis of currently published data.

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Застосування транексамової кислоти у лікуванні мелазми

Транексамова кислота (ТК) — давно відомий препарат, який вже тривалий час використовують для лікування або запобігання надмірної крововтрати. На початку 1950-х років було встановлено, що амінокислота лізин має здатність інгібувати активацію плазміногену, але цей ефект був занадто слабким для того, щоб застосовувати її у лікуванні фібринолітичних геморагічних станів. Перша згадка про застосування ТК у дерматології датована 1979 р.: вона показала хороший результат у лікуванні актинічного пруриго. У подальших дослідженнях *in vitro* було продемонстровано, що ТК має здатність блокувати меланогенез. Протягом 2010 р. були опубліковані результати низки досліджень з оцінки ефективності ТК у лікуванні меланодермії та еритематозно-телеангіектатичної розацеа.

Спочатку цей препарат призначали системно, але згодом через можливі рідкісні, але серйозні ускладнення він був протестований для місцевого застосування. У цьому разі ТК забезпечує аналогічні результати лікування без ризику побічних ефектів. Особливий інтерес до застосування ТК у лікуванні меланодермії зумовлений тим, що вона виявляє активність на різних рівнях. Насамперед ТК пригнічує активність опасистих клітин і, як наслідок, вивільнення гістаміну. На підставі узагальнення даних огляду сучасної літератури щодо застосування ТК при меланодермії з'ясовано, що цей активний інгредієнт забезпечує хорошу ефективність у тих випадках, коли немає задовільної терапії з незначними побічними явищами.

Існує три основних способи лікування меланодермії за допомогою ТК: пероральне і внутрішньошкірне введення та місцеве застосування. За даними проаналізованої літератури, найкращих результатів терапії можна досягти за допомогою внутрішньошкірного введення ТК (4 мг/мл на місяць) або місцевого застосування 3 % ТК (двічі на день).

На сучасному етапі доступні дані про застосування ТК є обмеженими з двох причин: по-перше, більшість досліджень проведено за участі представників народів Азії; по-друге, немає масштабного дослідження, в якому шляхом порівняльного аналізу оцінили б ефективність цих трьох різних способів уведення препарату, що дало б змогу підтвердити (або не підтвердити) наш аналіз даних сучасних публікацій.

Ключові слова: транексамова кислота, мелазма, меланогенез, шкіра.

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Использование транексамовой кислоты в лечении мелазмы

Транексамовая кислота (ТК) – давно известный препарат, который на протяжении длительного времени используется для лечения или предотвращения чрезмерной кровопотери. В начале 1950-х годов было установлено, что аминокислота лизин имеет свойство ингибировать активацию плазминогена, но этот эффект был слишком слабым для того, чтобы использовать ее для лечения фибринолитических геморрагических состояний. Первое упоминание о применении ТК в дерматологии датировано 1979 г.: она показала хороший результат в лечении актинического пруриго. В последующих исследованиях *in vitro* было продемонстрировано, что ТК имеет свойство блокировать меланогенез. В течение 2010 г. были опубликованы результаты целого ряда исследований, в которых проведена оценка эффективности ТК при меланодермии и эритематозно-телеангиэктатической розацеа.

Сначала препарат назначался системно, но вскоре из-за возможных редких, но серьезных осложнений он был протестирован для местного применения. В этом случае ТК обеспечивает аналогичные результаты лечения без риска побочных эффектов. Особый интерес к использованию ТК в лечении меланодермии обусловлен тем, что она проявляет активность на разных уровнях. В первую очередь ТК подавляет активность тучных клеток и, следовательно, высвобождение гистамина. На основании обобщения данных обзора современной литературы, касающейся применения ТК при меланодермии, было выяснено, что этот активный ингредиент позволяет достичь высокой эффективности в случае отсутствия удовлетворительной терапии с незначительными побочными эффектами.

Существуют три основных способа лечения меланодермии с помощью ТК: пероральное и внутрикожное введение, а также местное применение. Согласно данных проанализированной литературы, наилучших результатов терапии можно достичь при внутрикожном введении ТК (4 мг/мл в месяц) или при местном применении 3 % ТК (2 раза в день).

На современном этапе доступные данные об использовании ТК являются ограниченными по двум причинам: во-первых, большинство исследований проводились при участии представителей народов Азии; во-вторых, отсутствует масштабное исследование, в котором путем сравнительного анализа оценили бы эффективность этих трех различных способов введения препарата, что позволило бы подтвердить (или не подтвердить) наш анализ данных современных публикаций.

Ключевые слова: транексамовая кислота, мелазма, меланогенез, кожа.

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