

# CLINICAL STUDIES

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## COMPARATIVE EVALUATION OF THE EFFECTIVENESS AND SAFETY OF ACNE TREATMENT WITH SYSTEMIC ISOTRETINOIN IN MONOTHERAPY AND TOGETHER WITH COMBINED ORAL CONTRACEPTIVES IN WOMEN

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## СРАВНИТЕЛЬНАЯ ОЦЕНКА ЭФФЕКТИВНОСТИ И БЕЗОПАСНОСТИ ЛЕЧЕНИЯ АКНЕ У ЖЕНЩИН СИСТЕМНЫМ ИЗОТРЕТИНОИНОМ В МОНОТЕРАПИИ И СОВМЕСТНО С КОМБИНИРОВАННЫМИ ОРАЛЬНЫМИ КОНТРАЦЕПТИВАМИ

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**Objective.** To give a comparative evaluation of the effectiveness and safety of acne treatment with systemic isotretinoin in monotherapy and together with combined oral contraceptives in women.

**Materials and methods.** 65 women with severe papulo-pustular acne took part in the study. They were divided into two groups: group I consisted of 35 women who used systemic isotretinoin for acne in monotherapy; group II included 30 women who took systemic isotretinoin together with combined oral contraceptives. A comprehensive clinical and laboratory study was conducted. The study included a biochemical blood test to

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determine the lipid profile, liver transaminases, and hormonal homeostasis. The obtained results were analyzed using the methods of parametric and nonparametric statistics, the standard error ( $m$ ) was used in the calculations, the level of statistical significance was noted at  $p < 0.05$ .

**Results.** In women treated for acne with systemic isotretinoin in monotherapy relief occurs in 4 weeks, and complete clinical recovery in 24 weeks after the beginning of therapy; when using systemic isotretinoin together with combined oral contraceptives, relief is determined in 2 weeks, and complete clinical recovery in 16 weeks of treatment. The main side effects of systemic isotretinoin were cheilitis, skin xerosis, retinoic dermatitis and telogen alopecia. Cheilitis was revealed in the majority of patients in both groups equally. Xerosis of the skin, retinoic dermatitis and telogen alopecia were more often observed in the 1<sup>st</sup> group. In women of the 1<sup>st</sup> group, the level of progesterone was significantly higher and the level of estradiol was lower than in women of the 2<sup>nd</sup> group.

**Conclusions.** Systemic isotretinoin has shown high efficacy and safety in treatment for acne in women. Combined oral contraceptives normalize hormonal homeostasis, which helps to eliminate acne. When using systemic isotretinoin in combination with combined oral contraceptives, the main clinical effect occurs earlier, and adverse reactions are less frequent and less severe than in monotherapy. The combined use of systemic isotretinoin and combined oral contraceptives is the optimal method of acne treatment in women.

**Keywords.** Systemic isotretinoin, combined oral contraceptives, main clinical effect, side effect.

**Цель.** Дать сравнительную оценку эффективности и безопасности лечения акне у женщин системным изотретиноином в монотерапии и в сочетании с комбинированными оральными контрацептивами.

**Материалы и методы.** В исследовании приняли участие 65 женщин с тяжелыми папулопустулезными акне, которые составили две группы: I группа – 35 женщин, использующих для лечения акне системный изотретиноин в монотерапии; II группа – 30 женщин, применяющих системный изотретиноин в сочетании с комбинированными оральными контрацептивами. Проведено комплексное клиничко-лабораторное исследование, включающее биохимический анализ крови с определением показателей липидного спектра, печеночных трансаминаз, гормонального гомеостаза. Анализ полученных результатов выполнен с помощью методов параметрической и непараметрической статистики, при расчетах использовалась стандартная ошибка ( $m$ ), уровень статистической значимости был отмечен при  $p < 0,05$ .

**Результаты.** У женщин с акне при применении системного изотретиноина в монотерапии улучшение наступает через 4 недели, а полное клиническое выздоровление – через 24 недели от начала терапии; при использовании системного изотретиноина в сочетании с комбинированными оральными контрацептивами улучшение возникает через 2 недели, а полное клиническое выздоровление – через 16 недель лечения. Основными побочными эффектами системного изотретиноина являлись хейлит, ксероз кожи, ретиновый дерматит и телогеновая алопеция. Хейлит был отмечен у подавляющего большинства пациенток, одинаково в обеих группах. Ксероз кожи, ретиновый дерматит и телогеновая алопеция чаще наблюдались у женщин, применяющих системные ретиноиды в монотерапии. У женщин с акне, использующих системный изотретиноин в монотерапии, достоверно выше уровень прогестерона и ниже значение эстрадиола, чем у женщин, применяющих системный изотретиноин совместно с комбинированными оральными контрацептивами.

**Выводы.** Системный изотретиноин показал высокую эффективность и безопасность при лечении акне у женщин. Комбинированные оральные контрацептивы нормализуют гормональный гомеостаз, что способствует устранению акне. При применении системного изотретиноина совместно с комбинированными оральными контрацептивами основной клинический эффект наступает раньше, а побочные реакции встречаются реже и менее выражены, чем при монотерапии системным изотретиноином. Сочетанное использование системного изотретиноина и комбинированных оральных контрацептивов является оптимальным методом лечения акне у женщин.

**Ключевые слова.** Системный изотретиноин, комбинированные оральные контрацептивы, основной клинический эффект, побочное действие.

## INTRODUCTION

The name of dermatosis "acne" has ceased to be used with the definition of "youthful" for a long time, because this disease can proceed or even occur after pubertal age. Moreover, it is mainly observed among women [1; 2]. E.R. Araviyskaya marks that about 20 % of adult women are concerned about the appearance of acne on the chin before menstruation [3]. Systemic isotretinoin, hormonal therapy, antibacterial agents, and azelaic acid are used externally to treat acne among women [4]. Antibacterial therapy suppresses the activity of *C. acnes* and has a remarkable anti-inflammatory effect [5]. Azelaic acid has primarily anticomedogenic and keratolytic effects [6]. Combined oral contraceptives are predominantly used among hormonal preparations [7]. These combined oral contraceptives reduce absolute and relative hyperandrogenemia, contributing to the reduction of sebum production, which is a key factor in the progression of acne [8]. Systemic isotretinoin affects all components of acne pathogenesis: it inhibits the function of sebaceous glands, eliminates follicular hyperkeratosis and has antibacterial and anti-inflammatory effects [9]. It is important to remember that systemic isotretinoin is teratogenic, therefore, women should avoid pregnancy during treatment and for one month after its termination [10]. Many people use combined oral contraceptives for this purpose, the effect of which was mentioned above [11].

**The aim of the study** is to provide a comparative evaluation of the efficiency

and safety of acne treatment among women with systemic isotretinoin in monotherapy and in combination with combined oral contraceptives.

## MATERIALS AND METHODS

The retrospective study was conducted on the basis of the inpatient department of the regional skin and venereological dispensary of the Perm region and medical centers A2Med and „Genesis“. Sixty-five women with serious papulopustular acne in the age range of 20–35 years participated in the study. There were distinguished two groups. The first group consisted of 35 women using systemic isotretinoin of 0.5 mg/kg per day in monotherapy for acne treatment; the second group consisted of 30 women using systemic isotretinoin of 0.5 mg/kg per day in combination with combined oral contraceptives. The groups were comparable in social and somatic status, body weight and height, all were residents of the Perm region, and all gave voluntary informed consent to participate in the study. The exclusion criteria were serious endocrine pathology, gynecological diseases in anamnesis, cardiovascular diseases, liver and kidney pathology, smoking, alcoholism, use of external medications for acne treatment.

A comprehensive clinical and laboratory examination was conducted. There were studied the complaints and made anamnesis of the disease and life, assessed the general condition of the body, examination of skin and mucous membranes, general blood and urine tests, biochemical blood analysis with determination of lipid spec-

trum, hepatic transaminases, hormonal homeostasis. The results were analyzed using the methods of parametric and non-parametric statistics using Microsoft Excel and Statistica 5.1 for Windows (Stat Inc., USA). The standard error (m) was used in the calculations, and the level of statistical significance was noted at  $p < 0.05$ .

## RESULTS AND DISCUSSION

Most women with serious papulopustular acne, who receive systemic isotretinoin in monotherapy, have improvement after 4 weeks and complete clinical recovery after 24 weeks from the beginning of therapy. Most improvement occurs after 2 weeks and complete clinical recovery occurs after 16 weeks of treatment among women with serious papulopustular acne, who receive systemic isotretinoin in combination with combined oral contraceptives (Table 1).

The most common side effects of systemic isotretinoin in the course of treatment of serious papulopustular acne among women were cheilitis, xerosis, retinoid dermatitis, and telogen alopecia. Cheilitis was

observed among the vast majority of patients equally in both groups. Xerosis, retinoid dermatitis, and telogen alopecia were more frequently observed among women receiving systemic isotretinoin in monotherapy (Table 2).

Women with serious papulopustular acne who receive systemic isotretinoin in monotherapy have significantly higher progesterone level and lower estradiol value than women using systemic isotretinoin in combination with combined oral contraceptives (Table 3).

Combined oral contraceptives eliminate hyperandrogenemia, and this results in decreased production and normalization of sebum chemistry. In this process, follicular hyperkeratosis and inflammatory response of the pilosebaceous follicle are indirectly reduced. Thus, combined oral contraceptives enhance the primary effect of systemic isotretinoin. In addition, estrogens, which are part of combined oral contraceptives, have a softening and moisturizing effect on the skin, giving it elasticity and softness, which can smooth unwanted adverse reactions of systemic isotretinoin.

Table 1

### Specific features of the progression of the primary effect of systemic isotretinoin in combination with monotherapy and combined oral contraceptives (% $\pm$ m)

Primary clinical effect	Group I, $n = 35$	Group II, $n = 30$	$p$
Occurrence of improvement after 2 weeks	$22.9 \pm 7.1^*$	$73.3 \pm 8.1$	0.004
Occurrence of improvement after one month	$77.1 \pm 7.1^*$	$26.7 \pm 8.1$	0.004
Complete clinical recovery after 16 weeks	$14.3 \pm 5.9^*$	$80.0 \pm 7.3$	0.001
Complete clinical recovery after 24 weeks	$85.7 \pm 5.9^*$	$20.0 \pm 7.3$	0.001

Note: there were statistically significant differences with the group of women with serious papulopustular acne receiving systemic isotretinoin in combination with combined oral contraceptives,  $*p < 0.05$ .

Table 2

**Specific features of side effects during monotherapy of systemic isotretinoin and in combination with oral contraceptives (%  $\pm$  m)**

Side effect	Group I, <i>n</i> = 35	Group II, <i>n</i> = 30	<i>p</i>
Cheilitis	91.4 $\pm$ 4.7	86.6 $\pm$ 6.2	0.537
Xerophthalmia and conjunctivitis	14.3 $\pm$ 5.9	10.0 $\pm$ 5.5	0.540
Nasal hemorrhage	11.4 $\pm$ 5.4	10.0 $\pm$ 5.5	0.853
Xerosis	60.0 $\pm$ 8.3*	26.7 $\pm$ 8.1	0.007
Retinoid dermatitis	45.7 $\pm$ 8.4*	16.7 $\pm$ 6.8	0.012
Telogen alopecia	42.8 $\pm$ 8.4*	13.3 $\pm$ 6.2	0.009
Paronychia and onychodystrophy	8.6 $\pm$ 4.7	6.7 $\pm$ 4.6	0.774
Headache, depression	5.7 $\pm$ 3.9	10.0 $\pm$ 5.5	0.518
Arthralgias and myalgias	5.7 $\pm$ 3.9	6.7 $\pm$ 4.6	0.873
Anemia	5.7 $\pm$ 3.9	6.7 $\pm$ 4.6	0.873
Hyperlipidemia	11.4 $\pm$ 5.4	10.0 $\pm$ 5.5	0.853
Increasing of liver transaminase level	8.6 $\pm$ 4.7	6.7 $\pm$ 4.6	0.774

Note: there were statistically significant differences with the group of women with serious papulopustular acne receiving systemic isotretinoin in combination with combined oral contraceptives, \**p* < 0.05.

Table 3

**Characteristics of hormonal homeostasis among women with acne during treatment using systemic isotretinoin in monotherapy and in combination with oral contraceptives (%  $\pm$  m)**

Indicators of hormonal homeostasis	Group I, <i>n</i> = 35	Group II, <i>n</i> = 30	<i>p</i>
Absolute hyperandrogenemia	17.1 $\pm$ 6.4	6.7 $\pm$ 4.5	0.366
Hyperprogesteronemia	62.9 $\pm$ 8.2*	10.0 $\pm$ 5.5	0.001
Decreasing estradiol level in the blood	34.3 $\pm$ 8.0*	6.7 $\pm$ 4.5	0.006

Note: there were statistically significant differences with the group of women with serious papulopustular acne receiving systemic isotretinoin in combination with combined oral contraceptives, \**p* < 0.05.

### CONCLUSIONS

1. Systemic isotretinoin has shown high efficiency and safety in the process of treatment from acne among women.

2. Combined oral contraceptives normalize hormonal homeostasis, which helps to eliminate acne.

3. When systemic isotretinoin is used in combination with combined oral contraceptives, the primary clinical effect occurs earlier, and side effects are less frequent and less serious than with the use of systemic isotretinoin monotherapy.

4. The combined use of systemic isotretinoin and combined oral contraceptives

is the optimal treatment for acne among women.

## REFERENCES

1. Preneau S., Dreno B. Female acne – a different subtype of teenager acne? J. Eur. Acad. Dermatol. Venereol. 2012; 26 (3): 277–282. DOI: 10.1111/j.1468-3083.2011.04214.x
2. Elkin V.D., Kobernik M.Yu., Sedova T.G., Kuznecov I.D. Clinical and laboratory characteristics of acne tarda in women of the Perm region. *Permskij medicinskij zhurnal* 2022; 39 (6): 11–17 (in Russian).
3. Samcov A.V., Aravijskaya E.R. Akne i rozacea. Moscow: Farmtek 2021; 400 (in Russian).
4. Gollnick H. From new finding sin acne pathogenesis to new approaches in treatment. J. Eur. Acad. Dermatol. Venerol. 2015; 29 (5): 1–7. DOI: 10.1111/jdv.13186
5. Ryabova V.V., Koshkin S.V., Zaitseva G.A., Evseeva A.L. Character of distribution of immunological indicators in patients with average and severe forms of acne. *Immunopatologiya, allergologiya, infektologiya* 2017; 3: 75–78 (in Russian).
6. Leyden J.A. A review of the use of combination therapies for the treatment of acne vulgaris. J. Am. Acad. Dermatol. 2003; 49 (3): 200–210. DOI: 10.1067/s0190-9622(03)01154-x
7. Tan J.K., Bhate K. A global perspective on the epidemiology of acne. Br. J. Dermatol. 2015; 172 (1): 3–12. DOI: 10.1111/bjd.13462
8. Eichenfield D.Z., Jessica Sprague J., Eichenfield L.F. Management of acne vulgaris: a review. JAMA. 2021; 326 (20): 2055–2067. DOI: 10.1001/jama.2021.1763
9. Perlamutrov Yu.N., Olkhovskaya K.B. Clinical effectiveness and safety profile of systemic isotretinoin in acne therapy. *Klinicheskaya dermatologiya i venerologiya* 2020; 19 (5): 730–736. DOI: 10.17116/klinderma.202019051730 (in Russian).
10. Bagatin E., Sousa Costa C. The use of isotretinoin for acne – an update on optimal dosing, surveillance, and adverse effects. J. Expert. Rev. Clin. Pharmacol. 2020; 13 (8): 885–897. DOI: 10.1080/17512433.2020.1796637
11. Fallah H., Rademaker M. Isotretinoin in the management of acne vulgaris: practical prescribing. Int. J. Dermatol. 2021; 60 (4): 451–460. DOI: 10.1111/ijd.15089

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Kobernik M.Y. – contributed to the concept and design of the study, acquisition, analysis and interpretation of data; prepared the first version of the article.

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