Review Article

Oral Isotretinoin Treatment in Rhinoplasty: A Review

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ABSTRACT

The achievement of best outcome in rhinoplasty is very important for both of the patients and plastic surgeons. Since the skin characteristics (e.g. nasal thickness and sebaceous hypertrophy) has clear role on the result, many related interventions have been proposed in recent decades to gain an appropriate result. Accordingly, isotretinoin firstly introduced to treat some type of acne, has been suggested controversially to be used in rhinoplasty. Although the early uncertain studies implied on its side effects, the recent more powerful studies and evidences indicate that isotretinoin is remarkably effective to obtain proper outcome. Nevertheless, its prescription to patients need to be evaluated and personalized. More discussion on this regard are presented in the text.

KEYWORDS
Tretinoin; Rhinoplasty; Isotretinoin

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INTRODUCTION

Rhinoplasty is one of the most-common cosmetic procedures worldwide. According to the 2020 Plastic Surgery Statistics Report, the total expenditure of 352,555 performed rhinoplasty in US was more than 1.9 billion Dollars in a year. Females and 13-40 years old persons, constitute 81.5% and 67.74% of the cases, respectively; the groups who are more sensitive on their appearance [1]. Furthermore, the human nose has a complex and important physiologic role, so it is wise to preserve and even improve both of the beauty and function of this delicate organ during its aesthetic surgeries [2].

The wide terminology of rhinoplasty is considered for surgical and nonsurgical rhinoplasty which the earlier may be done as open or closed surgical strategies. For all types of rhinoplasty, many innovative techniques have been emerged, alongside with the classic ones, in recent decades. However, despite of any applied method and strategy, the result of rhinoplasty is very important for the patients, both aesthetically and functionally [3].

In addition to surgeon expertise, applied technic, availability of proper surgery environment and instruments, etc.; the patient's factors will influence on rhinoplasty outcome. For this reason pre evaluation of the patients is highly recommended to assess influencing factors on

rhinoplasty outcome like the patient's personality, medical background and especially skin quality [2].
The skin characteristics of thickness and subcutaneous soft tissues are growingly considered in outcomes of facial plastic surgeries. Moreover, acne is more prevalent in patients with a thick skin-soft tissue envelope and also in patients who are mostly request rhinoplasty; i.e. ages of adolescents and young adults. The patients with thick nasal skin are more prone to undesirable outcome of rhinoplasty like undefined nasal tip and deformities in supratip area [4]. So, it is recommended to pre evaluate and classify the patients. The different classifications are nearly similar. For example, Cobo et al [5] have excluded patients with thin nose skins and classified patients with thick skin to three types (Table 1). This classification was based on the skin characteristics, in order to do the best surgical and non-surgical management, both before and after the operation. The authors believe on treatment plans for each type of skins, both topically and surgically, which may be started from many months before the operation up to many months after operation [5].
Meanwhile, based on causative etiology and quality of skin, some authors consider easier classification:
a) Thickness of the nose skin due to sebaceous hypertrophy (Fig. 1-A). This type has large pores and significant sebaceous activity and seems to be equal to type III or somehow type II of Cobo's classification.
b) Inherent thickness of the dermis (Fig. 1-B). This skin is somewhat red and shiny and has a thick dermis with fewer sebaceous glands. It is equal to type I previously described classification [6].
Considering all of classifications, it is believed that skin thickness due to excessive sebaceous activity can be highly controlled by proper diet, use of Retin A and treatment with isotretinoin. In contrast in patient with inherent thickness in dermis, who has no sebaceous hyperactivity, this management will not be adequately effective and other modalities are needed to achieve best outcomes in rhinoplasty [5, 6].
As it was indicated previously, the prescription of isotretinoin in different type of skins thickness has been suggested to acquire best results of rhinoplasty. However, it has some controversies, therefore need to be widely explained.

Table 1: Clinical classification of patients according to nose skin quality

Types	Thickness	Elasticity	Oiliness	Acne, redness and pores*
Type I	Thick	Present	Absent	No acne or redness
Type II	Thick	Little elasticity	Present	Mild-to-moderate acne or acne-prone. Present open pores
Type III	Thick	No elasticity	Present	Present moderate-to-severe acne Possible moderate-to-severe redness Present open pores

* Note: Hyperpigmentation, telangiectasias, and other dyschromias may be seen in any of types.

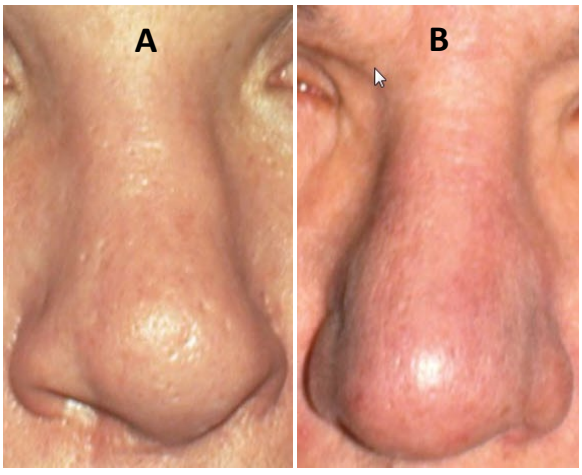

Figure 1: Two type of nose skin thickness: A. sebaceous over activity B. innate thickness of dermis

ISOTRETINOIN

As a retinoid derivative of vitamin A, the first oral containing product of isotretinoin (13-cis-retinoic acid) was approved by FDA on May 7, 1982 under the name of Accutane®. This small molecule mainly used in the treatment of severe recalcitrant nodular acne vulgaris (Fig. 2). While accutane has been discontinued now, isotretinoin oral capsule is available under the other brand names like absorica, amnesteem, claravis, myorisan, sotret, zenatane, etc in different dosage forms [7-9].

By increasing p53 expression and being effective on neutrophil-gelatinase-associated lipocalin (NGAL), isotretinoin has consequence on cell cycle, differentiation, survival and apoptosis, hence reduces sebum production and shrink sebaceous glands, prevents the blockage of pores and restricts growth of acne causing bacteria. Although it has limited or no tendency to bind retinol binding proteins (RBPs) and retinoic acid nuclear receptors (RARs) directly; its derivatives bind to the RAR-γ receptor which through that partly act on acne treatment. Furthermore, isotretinoin induces sebocytes apoptosis and diminish sebum production. It also decreases hyperkeratinization and comedones formation. Isotretinoin has no direct bactericidal effect, however, it reduces the size of sebum ducts and makes the microenvironment unfavorable for acne causing bacteria (*Cutibacterium acnes)*. Isotretinoin may augment immune mechanisms and adjust monocytes chemotaxis to decrease inflammation. It also increase levels of dermicidin (or proteolysis-inducing factor), an antimicrobial peptide of eccrine/sebaceous glands [10-12]. Meanwhile, it is suggested that isotretinoin may upregulate forkhead box class O (FoxO) transcription factors which may explain its unexplained actions [13].

The mean half-life of isotretinoin is 20 hours (ranges 7-39 hours). Isotretinoin is better absorbed with a high fat meal and has high serum protein bound (mainly albumin). It is metabolized in liver and converted to 5 active metabolites. After conjugation, isotretinoin and its metabolites are excreted in the urine and feces in equal amount; although 53-74% of its oral dose are eliminated unchanged in the feces [7, 8, 12].

Even one dose of isotretinoin is associated with major congenital malformations (in head and neck, heart, brain, etc), spontaneous abortion and premature birth. Thus, it is strongly contraindicated in pregnancy, probable pregnancy condition, under 12 years of age and also prohibited in breast feeding mothers [7-9]. Isotretinoin is only available under the iPLEDGE program in the United States which is a safety program to manage the risk of isotretinoin's teratogenicity and to minimize fetal exposure, [14].

DISCUSSION

The recalcitrant acne vulgareis was stated as the main indication of isotretinoin when it was introduced in early 1980s. However, many other disorders may be treated by this medication. The conditions which can be treated with isotretinoin includes nodulocystic acne vulgaris, milder acne vulgaris resistant to other medications, acne with scarring and psychological issues, acne conglobata, acne rosacea, acne fulminans, hidradenitis suppurativa, types of ichthyosis, cutaneous neoplasms, rhinophyma, sebaceous hyperplasia, etc. Although, the therapeutic dose of isotretinoin for dermatologic diseases ranges from 0.1 to 8.2 mg/kg/d, its usual prescription dose is 0.3 to 1 (up to 2) mg/kg/d, two-times a day for 15-24 weeks (up to 9 months) [11, 12, 15]. Because of the reported advantages and disadvantages, the combination of rhinoplasty and isotretinoin prescription has been in controversies. More detailes are presented as below.

Since the early introducing of oral isotretinoin in treatment of acne vulgaris, some side effects and complications have been reported for this drug. Beside of incommon osteal changes (e.g nasal osteophytes and skletal hyperostosis), many others

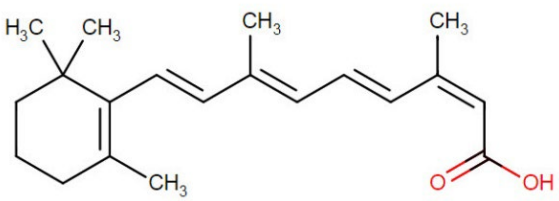

Figure 2: The chemical structure of isotretinoin (formula: $C_{20}H_{28}O_2$, weight: 300.4351)

Table 2: The adverse effects of isotretinoin

Variable	Common adverse effects	Uncommon but important adverse effects
Mucocutaneous	Xerosis Cheilitis Facial erythema Photosensitivity Pruritus Flare of acne Skin fragility, delayed healing Dermatitis Palmoplantar desquamation Nasal mucosal dryness Epistaxis Alopecia Nail dystrophy Paronychia Staphylococcus aureus infections	Hyperhidrosis Pyogenic granuloma Steven Johnson Syndrome/ Toxic epidermal necrolysis Urticaria/angioedema/anaphylaxis
Ocular	Dry eyes Ocular discomfort Blepharoconjunctivitis Hordeolum Chalazion	Corneal opacities Decreased dark adaptation Keratitis Decreased vision Myopia Photophobia Decreased color vision
Musculoskeletal	Myalgia Arthralgia	Uni-, oligo- or poly-arthritis Enthesopathy Sacroiliitis Lower back pain Hyperostoses Myopathy Rhabdomyolysis Premature epiphyseal closure
Biochemical	Increases in liver transaminases Leucopenia, neutropenia Elevated cholesterol and triglycerides	Thrombocytopenia Hyperuricaemia
Gastrointestinal		Diarrhoea Abdominal pain Pancreatitis Inflammatory bowel disease*
Psychiatric/ Neurologic	Headache Fatigue	Affective disorders, particularly depression* Suicidal ideation* Behavioural disturbances Benign intracranial hypertension Impaired hearing (rare reports) Tinnitus

* although the cases are reported, their association need to be approved by more evidences.

have been described in recent decades which are summerized in Table 2. Combining an antihistamine to isotretinoin regimen may decrease adverse effects and improve its efficacy [11, 16, 17].

On the other hand, the teratogenicity of isotretinoin is the most important adverse event. The overexpression of proapoptotic transcriptional factor of P53 and increase in apoptosis of neural crest cells may be the reason. Although the possibility of normal evolution of pregnancy is 65-85% , it is mandatory to confirm that the patient is not pregnant before and during the treatment period, up to at least

one month after drug secession [18]. Consequently, it is emphesized that oral isotretinoin prescription should be supervised by a dermatologists [6].

For many years, the conservative reports have signified that dermatosurgical procedures and local therapeutic or aesthetic interventions during oral isotretinoin treatment may be associoated with complications like healing abnormalities, keloid or hypertrophic scar production, etc., hence, the surgery should be done months prior to Isotrtinine prescription or delayed 6-12 months after its cessation. [4, 6, 19]. These early studies were mainly few, limited in sample size, low quality or case report [20]. Meanwhile, the surgical instruments and techniques were not developed as the present time. In contrast, the recent studies do not approve the previous inadequate and insufficient evidences and indicate on safety of oral isotretinoin in dermatologic surgeries [19].

In this regard, a published systematic review and experts' consensus recommended that isotretinoin usage maybe accompanied with side effects only for mechanical dermabrasion and fully ablative laser procedures. There are no sufficient evidence-based documents showing low dose treatment of isotretinoin may be connected with complications in other dermatosurgical procedures [21]. The safety of isotretinoin in dermatosurgeries and laser interventions has been supported by another multicentric study of Indian Association of Cutaneous Surgeons, too [22]. In addition, another review study explained systematic isotretinoin prescription is accompanied by low risk of poor healing and adverse effects in healthy patients who had skin operation. Nonetheless, it is mentioned that the combination of this medication in surgeries involving skeletal muscle flaps is chalengable and should be approached carefully; because there is danger of direct muscular damage and increased risk of necrosis [23]. Although the most common reported side effects of dryness of the skin, eyes, libs and intranasal mucosa can be easily resolved by lubricants [12], most of the reported side effects are dose dependent and predictable, so, personalization and dose adjustment are required. Meanwhile, to prevent significant but rare side effects (like depression and inflammatory bowel disease), the precise clinical monitoring and evaluation is recommended [24]. Consequently, to treat dermatosurgeries (including rhinoplasty) with isotretinoin, the complete explanation of the procedures, treatments, results and possible side effects should be discussed with the patients. Making an informed decision and obtaining a written consent form are highly suggested [21].

Despite of different introduced surgical or non surgical techniques in treatment of thick-skinned patients undergoing rhinoplasty, the outcome is not idealistic and may be accompanied by some complications. It has more importance in adolescents or young adults who are more prone to acne and simultaneously require rhinoplasty [12]. According to some clinical trials, 10-20 mg oral isotretinoin effectively improves skin elasticity, increases collage production, reduces wrinkles, pigmentation, actinic keratoses and pore size. It may be useful for sebaceous hyperplasia by dose of 0.14–1.0 mg/kg/d, too [15]. The ability of oral isotretinoin in reduction of nose size, skin thickness and oil, together with aforementioned effects have made it a proper candidate to be used in rhinoplasty in thick skinned patients with sebaceous over activity (type II and III of Cobo's classification). Additionally, it may also be helpful in recovering from acne through post rhinoplasty period [4]. A randomized placebo-controlled clinical trial by Sazgar et al. showed significant accelerated improvement in cosmetic outcome of rhinoplasty in isotretinoin treated cases; especially during early months [25]. This finding has been supported by the other study, too. The clinical trial of Yahyavi et al. indicated isotretinoin consumption in rhinnoplasty cause no evident disturbance in healing, recovery and internal nose structures, including hypertrophic tissues and cartilaginous deformities. The authors also believed that due to lesser oil production, the isotretinoin receiving patients experience no early detachment of the nose plaster or splint, which may result in severe inflammation of nose tip. On contrast, the stronger adhesion between nose skin and tape, beside the early weeks accelerated recovery, makes these patients more satisfied with the surgery outcome [26].

In addition, some experimental studies imply on this subject. For example, the impact of systemic isotretinoin on nasal skin thickness has been supported by high resolution ultrasonographic study of Yigit et al. which revealed oral isotretinoin significantly decreases the thickness of dermis and subcutaneous soft tissue at every nasal landmark, regardless of the treatment dose. However, the

minimum 4-month dose of 0.25 mg/kg/d of isotretinoin is needed to thin nasal tip dermis and soft tissue thickness at rhinion and glabella area. Besides, the elasticity can be increased significantly by at least 4 months' isotretinoin treatment, regardless of dose. They proposed that easier surgery planning and proper postoperative aesthetic outcome will be obtainable by low dose isotretinoin prescription in selected nasal thick skinned rhinoplasty candidates [4]. Therefore, the total increasing recent documents indicate that combination of oral isotretinoin in rhinoplasty is not only safe but may also provide notable outcome in sebaceous gland hyperplasia, acne scars and thick-skinned patients undergoing rhinoplasty or other facial plastic surgeries [4, 12].

CONCLUSION

Based on the recent evidences, the combination of isotretinoin in rhinoplasty makes the consequent of the surgery more appropriate. However the following important points should be considered. Isotretinoin is mainly effective in patients with thick nasal skins who has sebaceous hyperactivity. The best results will be achieved by its low dose for at least 4 months prescription. Meanwhile, because of its side effects, including the importance of teratogenicity, the isotretinoin treatment should be personalized and supervised by dermatologists. It means that all of the advantages and disadvantages of Isotrtinoin treatment and also the medical background of the patient should be evaluated all together. These items should be clealy explained to the patient, followed by making final decision and signing of writen consent form.

On the other hand, many vague points and items need to be answered and approved. So, it is wise to conduct additional integrated, prospective and well controlled clinical trials, with standard protocols and appropriate sample size, in order to clarify unclear subjects like best treatment dose and duration, the affective role of other probable variable and factors on results, etc. Moreover, the follow up of the cases is recommended to find any potential short and long term safety or hazards.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

REFERENCES

1. 2020 Plastic Surgery Statistics Report. AMERICAN SOCIETY OF PLASTIC SURGEONS; 2021.
2. Payam V, Behnam B. Contemporary Rhinoplasty Techniques. In: Mohammad Hosein Kalantar M, editor. A Textbook of Advanced Oral and Maxillofacial Surgery. Rijeka: IntechOpen; 2015. p. Ch. 31.
3. Nocini R, Chirumbolo S, Pirayesh A, et al. A Systematic Review and Meta-Analysis of Rhinoplasty Using the Rhinoplasty Outcome Evaluation Scale. *Ann Maxillofac Surg* 2022 Jan-Jun;**12**(1):60-8.
4. Yigit E, Rakici IT, Seden N, Manav V, Kaygisiz I, Yigit O. The Impact of Isotretinoin Therapy on the Nasal Skin Thickness and Elasticity: An Ultrasonography and Elastography Based Assessment in Relation to Dose and Duration of Therapy. *Aesthetic Plast Surg* 2022 Aug;**46**(4):1760-70.
5. Cobo R, Camacho JG, Orrego J. Integrated Management of the Thick-Skinned Rhinoplasty Patient. *Facial Plast Surg* 2018 Feb;**34**(1):3-8.
6. Rhinoplasty in Patients with Thick Skin. Plastic Surgery key, Fastest Plastic Surgery & Dermatology Insight Engine. Mar 11, 2016 ed: Reconstructive surgery; 2023.
7. Fei L, Bilal M, Qamar SA, et al. Nano-remediation technologies for the sustainable mitigation of persistent organic pollutants. *Environ Res* 2022;**211**:113060.
8. Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res* 2018 Jan 4;**46**(D1):D1074-d82.
9. Drugs.com. Isotretinoin. October 12, 2021 ed: drugs.com; 2022.
10. Layton A. The use of isotretinoin in acne. *Dermatoendocrinol* 2009 May;**1**(3):162-9.
11. Greydanus DE, Azmeh R, Cabral MD, Dickson CA, Patel DR. Acne in the first three decades of life: An update of a disorder with profound implications for all decades of life. *Dis Mon* 2021 Apr;**67**(4):101103.
12. Cobo R, Vitery L. Isotretinoin Use in Thick-Skinned Rhinoplasty Patients. *Facial Plast Surg* 2016 Dec;**32**(6):656-61.
13. Melnik BC. Isotretinoin and FoxO1: A scientific hypothesis. *Dermatoendocrinol* 2011 Jul;**3**(3):141-65.
14. iPLEDGE REMS committed to pregnancy prevention. 2021 [cited 2022 December 27]; Available from: https://ipledgeprogram.com/#Main
15. Chu S, Michelle L, Ekelem C, Sung CT, Rojek N, Mesinkovska NA. Oral isotretinoin for the treatment of dermatologic conditions other than acne: a systematic review and discussion of future directions. *Arch Dermatol Res* 2021 Aug;**313**(6):391-430.
16. Fallah H, Rademaker M. Isotretinoin for acne

vulgaris - an update on adverse effects and laboratory monitoring. *J Dermatol Treat* 2022 Aug;**33**(5):2414-24.
17. Novick NL, Lawson W, Schwartz IS. Bilateral nasal bone osteophytosis associated with short-term oral isotretinoin therapy for cystic acne vulgaris. *Am J Med* 1984 Oct;**77**(4):736-9.
18. Bagatin E, Costa CS. The use of isotretinoin for acne - an update on optimal dosing, surveillance, and adverse effects. *Expert Rev Clin Pharmacol* 2020 Aug;**13**(8):885-97.
19. Mysore V, Omprakash HM, Khatri GN. Isotretinoin and dermatosurgical procedures. *Indian J Dermatol Venereol Leprol* 2019 Jan-Feb;**85**(1):18-23.
20. Allen BC, Rhee JS. Complications associated with isotretinoin use after rhinoplasty. *Aesthetic Plast Surg* 2005 Mar-Apr;**29**(2):102-6.
21. Spring LK, Krakowski AC, Alam M, et al. Isotretinoin and Timing of Procedural Interventions: A Systematic Review With Consensus Recommendations. *JAMA Dermatol* 2017 Aug 1;**153**(8):802-9.
22. Mahadevappa OH, Mysore V, Viswanath V, et al. Surgical Outcome in Patients Taking Concomitant or Recent Intake of Oral Isotretinoin: A Multicentric Study-ISO-AIMS Study. *J Cutan Aesthet Surg* 2016 Apr-Jun;**9**(2):106-14.
23. Ungarelli LF, Hetem CM, Farina Junior JA. Is It Safe to Operate on Patients Taking Isotretinoin? *Aesthetic Plast Surg* 2016 Feb;**40**(1):139-48.
24. On SC, Zeichner J. Isotretinoin updates. *Dermatol Ther* 2013 Sep-Oct;**26**(5):377-89.
25. Sazgar AA, Majlesi A, Shooshtari S, Sadeghi M, Sazgar AK, Amali A. Oral Isotretinoin in the Treatment of Postoperative Edema in Thick-Skinned Rhinoplasty: A Randomized Placebo-Controlled Clinical Trial. *Aesthetic Plast Surg* 2019 Feb;**43**(1):189-95.
26. Yahyavi S, Jahandideh H, Izadi M, Paknejad H, Kordbache N, Taherzade S. Analysis of the Effects of Isotretinoin on Rhinoplasty Patients. *Aesthet Surg J* 2020 Nov 19;**40**(12):Np657-np65.