Isotretinoin-induced epistaxis among acne vulgaris patients

A cross sectional study from Saudi Arabia

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ABSTRACT

الأهداف: تقييم انتشار وعوامل الخطر المرتبطة بنزيف الأنف المرتبط بالإيزوتريتينوين بين مرضى حب الشباب.

المنهجية: من خلال دراسة التعرض الرجعية لعدد 230 مريضًا سعوديًا تلقوا الإيزوتريتينوين لعلاج حب الشباب في الدراسة. تم استخدام استبيان عبر الإنترنت لجمع البيانات المتعلقة بالتركيبة السكانية والأحداث السلبية المرتبطة بالعلاج.

النتائج: وجد أن انتشار نزيف الأنف الناجم عن الإيزوتريتينوين بلغ 45.2%، وهو ما يمثل زيادة بمقدار 5 أضعاف في نزيف الأنف، مقارنة بالأساسي. تم الإبلاغ عن نزيف الأنف من قبل 90% من المرضى الذين لديهم تاريخ سابق من نزيف الأنف. أفاد المرضى الذين يعانون من «انسداد الأنف» بانتشار بنسبة 68.8%. كان لدى الغالبية العظمى من المرضى شكل خفيف من نزيف الأنف، بينما أفاد ما يقرب من ربعهم بحدة معتدلة. أبلغت مجموعة فرعية صغيرة من المرضى عن نزيف حاد يستدعي زيارة غرفة الطوارئ ونقل الدم. 93.5% و61.3% من المرضى لم ينصحهم أطباء الجلدية بأهمية استشارة أخصائي الأنف والأذن والحنجرة وترطيب الأنف على التوالي أثناء تناول عقار أيزوتريتينوين.

الخلاصة: إن انتشار نزيف الأنف الناجم عن عقار أيزوتريتينوين مرتفع بشكل ملحوظ بين المرضى السعوديين؛ ويمكن أن تؤثر هذا المضاعفات على ما يقرب من نصف المرضى الذين يتلقون هذا الدواء. وتشمل عوامل الخطر الرئيسية التاريخ السابق للنزيف الأنفي، وانسداد الأنف، وضعف الوعي بشأن الآثار الجانبية الأنفية لنزيف الأنف والتدابير الوقائية الخاصة به. يجب وصف عقار أيزوتريتينوين بحكمة من قبل أطباء الجلدية، بالتشاور مع أخصائي الأنف والأذن والحنجرة، مع تثقيف المريض بشكل كافٍ بشأن الآثار الجانبية الأنفية المحتملة والخطوات اللازمة للتخفيف منها.

Objectives: To assess the prevalence and risk factors of isotretinoin-related epistaxis, among patients of acne vulgaris.

Methods: A retrospective cohort of 230 Saudi patients who received isotretinoin for treatment of acne vulgaris, was included in the study. An online questionnaire was used to collect data regarding demographics and treatment-related adverse events.

Results: The prevalence of isotretinoin-induced epistaxis was found to be 45.2%, which was a 5-fold increase in epistaxis, versus baseline. Epistaxis was reported by 90% patients who had a prior history of nasal bleeding. Patients with 'obstructed nose', reported a prevalence of 68.8%. The large majority of patients had a mild form of epistaxis, while nearly one-fourth reported moderate severity. A small subgroup of patients reported severe epistaxis warranting emergency room (ER) visits and blood transfusion. A staggering 93.5% and 61.3% patients were not advised by their dermatologists, regarding the importance of an ear-nose-throat (ENT) specialist consultation and nasal moisturization respectively, while taking isotretinoin.

Conclusion: The prevalence of isotretinoin-induced epistaxis is significantly high among Saudi patients; the complication can affect nearly half of the patients receiving this drug. Key risk factors include a prior history of nasal bleeding, nasal obstruction, poor awareness regarding the nasal adverse effects of epistaxis and its preventive measures. Isotretinoin should be prescribed judiciously by dermatologists, in consultation with ENT specialists, and with adequate patient education regarding its potential nasal adverse effects and steps to mitigate the same.

Keywords: Isotretinoin, epistaxis, acne vulgaris, nasal obstruction, nasal dryness, Saudi Arabia

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The occurrence of an ugly "pimple" on the face, or an irritating "zit", or an unsightly nodule, is one of the most frequently encountered skin disorders; it is caused by a condition called acne vulgaris, estimated to affect 9.4% of the global population. It is characterized by hyperseborrhoea, abnormal keratinization and proliferation of the causative pathogen *Propionibacterium Acnes* (*P. Acnes*). This results in inflammation of the cutaneous microenvironment. Heredity and environmental factors are also implicated in the etiology of acne.[1,2]

From the large repertoire of oral and topical anti-acne treatments currently available, the most promising and efficacious outcomes have been reported with the use of isotretinoin (13-cis-retinoic acid), which is a derivative of vitamin A. It is a widely prescribed treatment for acne vulgaris, especially for the more resistant, severe or refractory forms. It inhibits sebaceous gland activity, arrests hyperkeratinization and promotes comedolysis. This, in turn, suppresses *P. Acnes* activity and reduces cutaneous inflammation. This achieves early symptomatic benefit, regresses existing acne and prevents new acne formation.[3]

Nevertheless, the brilliant efficacy of isotretinoin in treating acne is often hampered by concerns regarding its safety profile. Cheilitis, xerophthalmia, conjunctivitis, nasal dryness and obstruction, epistaxis, and photosensitivity are some of the frequently reported adverse effects. In addition to these, metabolic derangements, depression and teratogenicity have also been reported.[4]

Most often, patients receiving isotretinoin, are ignorant of these side effects of the drug and of preventive measures required to mitigate these deleterious effects. Past evidence from Saudi Arabia has highlighted this problem of poor patient awareness regarding the side effects of isotretinoin therapy. Lack of proper patient education by dermatologists, regarding the safety concerns of isotretinoin, represents a key cause of poor patient awareness.[3] Even though epistaxis is one of the commonest side effects of isotretinoin, we did not come across clinical studies focused on the prevalence of epistaxis, among the currently large pool of isotretinoin users in Saudi Arabia. In our view, epistaxis is also one of the most bothersome side effects of isotretinoin, as a sudden nasal bleed can trigger panic and scare among uninformed patients and their families. The nasal bleed could be aggravated by underlying systemic disorders or other ongoing medications. We also believe this to be a growing concern for ENT specialists, given the high prevalence of acne and related isotretinoin use, in Saudi Arabia.

Therefore, the current study was carried out to elucidate the prevalence of epistaxis and its associated risk factors, among acne vulgaris patients who were treated with isotretinoin, at a leading Saudi hospital. We believe this could provide a fresh assessment of isotretinoin-induced epistaxis in a Saudi cohort and would also throw light on Saudi patients' awareness regarding this frequent complication of isotretinoin therapy. We believe the results of this study could prompt ENT specialists and dermatologists in other regions of Saudi Arabia, to investigate isotretinoin-induced epistaxis, through larger, multicentric studies.

Methods. This was a retrospective, analytical, cross sectional study conducted among acne vulgaris patients, who received oral isotretinoin treatment at a leading hospital in Saudi Arabia, from October 2023 to March 2024. The study aimed to assess the prevalence and risk factors of isotretinoin-induced epistaxis among these patients. All acne patients in the hospital database, who received isotretinoin during this period, were invited to participate in this study through email invitations, followed up by telephonic reminders. The objectives of the study and eligibility criteria were explained to the patients. Informed consent was obtained via e-mails. The ethics committee at the hospital approved the study. The study was conducted in accordance to the principles of the declaration of Helsinki.

The inclusion criteria were patients with acne vulgaris who received oral isotretinoin for treatment. The exclusion criteria were patients with nasal surgery, allergic or non-allergic rhinitis and chronic sinusitis, upper respiratory tract infection in the last 4 weeks, any history of topical or other systemic drug use, smoking and septum deviation, concha hypertrophy, nasal polyp, chronic otitis media, radiation therapy to the head and neck, and bleeding disorders or other systemic disease.

The prevalence of epistaxis in the overall study cohort was the primary outcome measure. The other outcome measures comprised the prevalence of epistaxis in the subgroups of patients with dry nose, obstructed nose and those with a prior history of nasal bleed. The study also aimed to assess participants' awareness regarding the nasal adverse effects of isotretinoin and the knowledge of basic precautions needed to minimize these effects.

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The study employed an in-house questionnaire developed by doctors in the ENT department, which was subsequently reviewed and approved by senior ENT consultants and the head of the department. The questionnaire was sent online to all eligible participants, in English and Arabic. It contained objective questions regarding relevant demographic information like age, gender, marital status and duration of therapy. It included questions regarding adverse effects (AEs) like nasal dryness, nasal obstruction, epistaxis, cheilitis, xerophthalmia, photosensitivity and other AEs experienced by participants while using isotretinoin. The questionnaire also had questions pertaining to the details of epistaxis episodes like intensity, frequency, bleeding duration, need for emergency room (ER) consultation, need for blood transfusion and anemia. Based on the clinical experience and acumen of our experienced ENT team, the intensity and frequency of epistaxis were classified as first, second and third degree. The definitions of the grades of intensity were as follows: Grade 1 - slight blood stains on the handkerchief; Grade 2 – blood-soaked handkerchief; Grade 3 - bowl or similar utensil necessary to collect the oozing blood. Similarly, the definition of the grades of frequency were as follows: Grade 1 - less than once a week; Grade 2 - few times a week; Grade 3 - more than once a day. Finally, the questionnaire assessed participants' knowledge and awareness levels regarding precautionary measures to be exercised, for managing and minimizing nasal adverse effects, during isotretinoin use.

The duly filled copies of the online questionnaire were e-mailed back to the research team by the participants and were subsequently saved in a confidential electronic repository.

Statistical analysis. The raw data obtained from the questionnaire responses was analyzed as per the study objective. Continuous variables were expressed as mean and standard deviation (SD), according to normal distribution. Categorical data were described in numbers (percentages). Comparison of continuous variables was done using the unpaired t-test for independent samples, and categorical variables were compared using Fisher's exact test. Statistical analyses were performed using the Statistical Package for Social Sciences software, v. 17.0 for Windows (SPSS Inc., Chicago, Ill., USA). Values of $p<0.05$ were considered statistically significant.

Results. A total of 265 patients were identified from the hospital database who received oral isotretinoin during the study period, for treatment of acne vulgaris. All of these patients were invited to participate in the study. Of these, five patients did not consent to participate citing personal reasons. From the remaining 260 patients who consented to participate, 30 patients did not meet the inclusion criteria. Hence, a total of 230 patients were finally enrolled into the study. The retrospective study sample was highly skewed towards the female gender, as the large majority of 85.7% participants were females ($p<0.0001$). However, except for the number of participants, the male and female subgroups in the study, did not differ significantly with respect to any other demographic parameters. The study population was young, in its mid-twenties, with the mean age being around 25-26 years; the majority of them were unmarried. Most patients in the study had received isotretinoin therapy for a period of five to six months. Table 1 summarizes these demographic features across the male and female subgroups in the study.

The large majority comprising 82.2% patients experienced ≥1 known side effects of isotretinoin therapy. Females in the study experienced a significantly higher number of AEs. A significantly higher number of participants experienced isotretinoin-related xerophthalmia, dry lips, dry nose and obstructed nose ($p<0.0001$ for each of these). Table 2 presents a summary of treatment-related AEs in the study.

Isotretinoin-related epistaxis was reported by 104 participants, which meant a prevalence of 45.2% in the study population. The difference between the number of patients with and without epistaxis was not statistically significant. Among the twenty patients who had a prior history of nasal bleeding at baseline, a staggering 90% (18/20) patients experienced epistaxis with the use of isotretinoin; this clearly indicated that patients with a history of nasal bleed are significantly more vulnerable to isotretinoin induced epistaxis. The prevalence of epistaxis was comparable among patients with and without dry nose, however, among study

Table 1 - Summary of key demographic parameters of study participants (N=230).

Variable	Male group n (%)	Female group n (%)	*P*-value
Number of patients (%)	33 (14.3%)	197 (85.7%)	<0.0001*
Age (years), mean±SD	25.45±8.1	25.96±5.2	0.6342
Marital state			
Single	22 (66.6%)	151 (76.6%)	
Married	9 (27.3%)	39 (19.8%)	0.2390
Divorced	2 (6.1%)	7 (3.6%)	
Duration of isotretinoin therapy (months), mean±SD	6.01 ± 3.5	5.41 ± 3.1	0.3222

*Statistically significant difference between male and female groups ($p<0.05$); *P*-value for scale variables was calculated using unpaired t-test (for Mean ± standard deviation [SD]), and using Fisher's exact test (for number and %)

Table 2 - Summary of isotretinoin-related key adverse events.

Variable	Total study population (N=230)	*P*-value*	Male group (n=33) n (%)	Female group (n=197) n (%)	*P*-value§
Reported ≥1 adverse effects of isotretinoin therapy					
Yes	189 (82.2%)	<0.0001*	23 (69.7%)	166 (84.3%)	0.0289§
No	41 (17.8%)		10 (30.3%)	31 (15.7%)	
Increase skin sensitivity to sunlight					
Yes	127 (55.2%)	0.1550	17 (51.5%)	110 (55.8%)	0.7069
No	103 (44.8%)		16 (48.5%)	87 (44.2%)	
Xerophthalmia					
Yes	177 (77%)	<0.0001*	21 (63.6%)	156 (79.2%)	0.0716
No	53 (23%)		12 (36.4%)	41 (20.8%)	
Average dose causing Xerophthalmia (mg)	29.1 ± 10	-	32 ± 8.3	30.77 ± 9.36	0.5781
Dry lips					
Yes	213 (92.6%)	<0.0001*	31 (93.9%)	182 (92.4%)	0.7522
No	17 (7.4%)		2 (6.1%)	15 (7.6%)	
Average dose causing dry lips (mg)	30.9 ± 9.2	-	28.33 ± 9.1	29.18 ± 10.2	0.6683
Obstructed nose					
Yes	77 (33.1%)	<0.0001*	10 (30.3%)	66 (33.5%)	0.8715
No	154 (66.9%)		23 (69.7%)	131 (66.5%)	
Average dose causing obstructed nose (mg)	32.02 ± 9.4	-	28.88 ± 9.3	32.6 ± 9.3	0.2696
Dry nose					
Yes	155 (67.4%)	<0.0001*	20 (60.6%)	135 (68.5%)	
No	75 (32.6%)		13 (39.4%)	62 (31.5%)	0.4853
Average dose causing dry nose (mg)	32.13 ± 9.3	-	29.5 ± 7.6	31.9 ± 9.3	0.2836

*Statistically significant difference between variables in the total study population ($p<0.05$).
§Statistically significant difference between male and female groups ($p<0.05$).

participants with 'obstructed nose', the prevalence of epistaxis was nearly 23% higher than the overall study population and more than double as compared to those who did not report nasal obstruction (68.83% versus 31.17%). Of the 104 patients who reported epistaxis, the majority had a mild form of the complication, with 73.1% and 68.3% reporting first degree severity and frequency of epistaxis, as per the definitions of the in-house questionnaire. Due to the mild presentation of epistaxis, the large majority of patients bled <10 minutes, did not need any hospitalization, emergency consultation or blood transfusion and also did not experience any anemia. No significant gender-based differences were noted regarding the occurrence and pattern of epistaxis.

While the majority of epistaxis episodes in the study were mild, we cannot completely discount the small proportion of study patients who did experience a more severe form of isotretinoin-induced epistaxis. Nearly 27% patients experienced epistaxis of moderate or second degree severity, while 23% patients reported a moderate frequency of epistaxis. It is noteworthy that 8.6% patients had third degree frequency of epistaxis and a period of bleeding that ranged between 10-30 minutes. Seven patients needed to be taken into the ER for management of epistaxis, while two needed to undergo blood transfusion post epistaxis. Table 3 summarizes the prevalence and pattern of isotretinoin related epistaxis in the study.

It is noteworthy that study participants reported poor awareness levels regarding precautionary measures to be exercised while on oral isotretinoin therapy. The most preliminary precaution of moisturizing the nasal passage while using isotretinoin was not communicated to 61.3% participants by their dermatologists. A staggering 93.5% participants were not informed by their dermatologists to seek at least one medical consultation from an ENT specialist while using oral isotretinoin. Nearly half the study participants were aware on the need to use a nasal moisturizer, however, this awareness was not created through dermatologists' counseling, it rather came from patients' self reading about the effects of isotretinoin. On the other hand, >50% patients were completely ignorant regarding the importance of nasal moisturization. This awareness was notably lower among male participants as compared to females. Table 4 summarizes the awareness levels among study participants regarding precautions to be taken with isotretinoin therapy.

Discussion. The gender and age demographics of our study sample seem to be well in line with previous

Table 3 - Summary of isotretinoin-related epistaxis in the study population.

Variable	Total study population (N=230)	*P*-value*	Male group (n=33)	Female group (n=197)	*P*-value§
Prevalence of epistaxis					
Yes	104 (45.2%)	0.2030	14 (42.4%)	90 (45.7%)	0.8505
No	126 (54.8%)		19 (57.6%)	107 (54.3%)	
Past history of nose bleeding before isotretinoin therapy					
Yes	20 (8.7%)	<0.0001*	3 (9.1%)	17 (8.6%)	0.9306
No	210 (91.3%)		30 (90.9%)	180 (91.4%)	
Prevalence of epistaxis among patients with prior history of nasal bleeding					
Yes	18/20 (90.0%)	<0.001*	3 (15%)	15 (75%)	<0.05§
No	2/20 (10.0%)		1 (5%)	1 (5%)	
Prevalence of epistaxis among patients with dry nose					
Yes	75/155 (48.4%)	<0.05*	34 (21.9%)	41 (26.5%)	0.9411
No	80/155 (51.62%)		45 (29%)	35 (22.6%)	
Prevalence of epistaxis among patients with obstructed nose					
Yes	53/77 (68.83%)	<0.001*	22 (28.6%)	31 (40.3%)	0.05*
No	24/77 (31.17%)		5 (6.5%)	19 (24.7%)	
Severity of epistaxis					
1st degree	76/104 (73.1%)	<0.0001*	10/14 (71.4%)	66/90 (73.3%)	0.8812
2nd degree	28/104 (26.9%)		4/14 (28.6%)	24/90 (26.7%)	
Frequency of epistaxis					
1st degree	71/104 (68.3%)		11/14 (78.6%)	60/90 (66.7%)	
2nd degree	24/104 (23.1%)	<0.0001*	2/14 (14.3%)	22/90 (24.4%)	0.6584
3rd degree	9/104 (8.6%)		1/14 (7.1%)	8/90 (8.9%)	
Duration of epistaxis					
Less than 10 minutes	95/104 (91.4%)	<0.0001*	12/14 (85.7%)	83/90 (92.2%)	0.7682
10-30 minutes	9/104 (8.6%)		2/14 (14.3%)	7/90 (7.8%)	
Need of blood transfusion after epistaxis					
Yes	2/104 (1.9%)	<0.0001*	0/14 (0%)	2/90 (2.2%)	0.5733
No	102/104 (98.1%)		14/14 (100%)	88/90 (97.8%)	
Management of epistaxis in emergency room					
Yes	7/104 (6.7%)	<0.0001*	2/14 (14.3%)	5/90 (5.6%)	0.5225
No	97/104 (93.3%)		12/14 (85.7%)	85/90 (94.4%)	
Need for hospital admission for managing epistaxis					
Yes	2/104 (1.9%)	<0.0001*	0/14 (0%)	2/90 (2.2%)	0.5733
No	102/104 (98.1%)		14/14 (100%)	88/90 (97.8%)	

Values are presented as number and (%). *Statistically significant difference between variables in the total study population ($p<0.05$). §Statistically significant difference between male and female groups ($p<0.05$).

Table 4 - Awareness of precautionary measures during the use of isotretinoin.

Variable	Total study population (N=230)	*P*-value*	Male group (n=33)	Female group (n=197)	*P*-value§
Dermatologist advised to visit an ENT doctor, at least once, while using isotretinoin					
Yes	15 (6.5%)	<0.0001*	0	5 (7.6%)	0.1368
No	215 (93.5%)		33 (100%)	182 (92.4%)	
Dermatologist advised to put moisturizing ointments for the nose while using isotretinoin?					
Yes	89 (38.7%)	0.0029*	13 (39.4%)	76 (38.6%)	1.0000
No	141 (61.3%)		20 (60.6%)	121 (61.4%)	
Personal awareness of the need to moisten your nose while using isotretinoin?					
Yes	108 (47%)	0.4796	11 (33.3%)	97 (49.2%)	0.1308
No	122 (53%)		22 (66.7%)	100 (50.8%)	

Values are presented as number and (%). *Statistically significant difference between variables in the total study population ($p<0.05$). §Statistically significant difference between male and female groups ($p<0.05$). ENT: ear-nose-throat

research that shows a 2.5 times higher proportion of dermatology visits, among adult females aged >20 years, compared to males, for treatment of acne. In the current study too, the large majority of 85.7% participants were females (p<0.0001), in their mid-twenties.[6]

A whopping 82.2% patients in the study reported ≥1 commonly known, isotretinoin-related adverse effect like nasal dryness, obstruction, epistaxis, cheilitis, xerophthalmia and photosensitivity. This seems in line with past evidence that has demonstrated such adverse effects in a large proportion of isotretinoin users. 4 A significantly higher proportion of females in the study experienced isotretinoin-related adverse events, versus their male counterparts. This finding also resonates with past evidence that isotretinoin-induced adverse effects have been reported more frequently in females, as compared to males.[7]

In the current study, the prevalence of isotretinoin-induced epistaxis was 45.2%. The prevalence demonstrated in this study, is comparable to previously published prevalence of 47.2% by Brzezinski et al[8] and 40% by Gorpelioglu et al.[9] However, some previous reports have shown a lower prevalence than the current study. Blasiak et al[10] reported epistaxis in 37.9% patients who used isotretinoin. In contrast to this, Ertam et al[11] reported a lower prevalence of 23.1% while Tasli et al[12] reported a prevalence of merely 19%, among cohorts of isotretinoin users. On the contrary, Alzoubi et al[13] reported the prevalence of isotretinoin-induced epistaxis to be 55.4%, which is notably higher than the current study and higher than most previous studies.[13] We believe that this variation in prevalence figures between various studies is attributable to multiple factors like differences in sample size, demographics, statistical methods and study design. In our view, the most optimal approach to obtain a precise estimation of isotretinoin-induced epistaxis, would be through large scale, multi-centric, well-controlled, prospective clinical trials on this subject.

In the current study, merely 20 out of 230 participants had a history of nasal bleed before initiating isotretinoin. However, with isotretinoin treatment, a 5-fold increase was noted and this number rose to 104. This rise in epistaxis seems to be in congruence with the known nasal adverse effect profile of isotretinoin, as well as wsith the findings of past evidence. Tasli et al,[12] demonstrated a >5-fold increase of epistaxis, between pre and post isotretinoin levels, with the mean score of epistaxis rising from 0.35 at baseline to 2.26 post-3-months of isotretinoin. This underlines the potential of isotretinoin to cause a significant increase in the risk of epistaxis. Therefore, we emphasize that patients need to be educated about the safety profile of isotretinoin, with special emphasis on frequently reported nasal adverse effects, and be made aware about preventive measures to minimize these side effects.

We conducted subgroup analysis to further determine the prevalence of epistaxis among participants with a 'past history of epistaxis' and among those who experienced symptoms of 'dry nose' and 'obstructed nose'. As expected, the prevalence of epistaxis among these subgroups was notably higher in comparison to the overall study sample. Ninety percent patients who had a prior history of nasal bleeding, reported isotretinoin-induced epistaxis during the study period. This clearly highlights 'past history of nasal bleed' as a potential risk factor for epistaxis during isotretinoin treatment. Hence, we reiterate that isotretinoin should be prescribed with due caution in these patients and with proper education and counseling regarding its nasal adverse effects.[14]

Dry nose, per se, did not significantly increase the prevalence of epistaxis in this study. In fact, the prevalence of epistaxis in the 'dry nose' subgroup closely resembled the prevalence in the overall study population. However, it is a well-known fact that nasal dryness can lead to nasal obstruction, which in turn, can trigger epistaxis. In the 'obstructed nose' subgroup of this study, prevalence of epistaxis was 23% higher than the overall study population and more than double as compared to those who did not report nasal obstruction (68.8% versus 31.2%). These findings clearly highlight the fact that as nasal dryness progresses to cause nasal obstruction, it can significantly escalate the risk and occurrence of epistaxis.[12]

The large majority of participants who had epistaxis during the study period, reported a mild form of the complication, which could be classified as first-degree severity and frequency, as per the definitions of the in-house questionnaire. A staggering >90% participants reported that their epistaxis episodes lasted less than 10 minutes and did not warrant any urgent medical consultation or blood transfusion. The mild form of epistaxis was seen despite the fact that patients received an average 30 mg of oral isotretinoin daily for nearly six months. In our view, this mild pattern of epistaxis can be attributed to the study's exclusion criteria, to a certain extent. Patients with chronic systemic disorders, systemic drugs and pre-existing nasal or airway pathology were excluded from the study. These factors can escalate bleeding risk in a real world setting; their exclusion could have impacted the severity of epistaxis seen in the study.[15-17] Nevertheless, it is widely known that mild epistaxis is mostly self-limiting and manageable,

in the absence of underlying aggravating factors.[14] This reiterates the need to document a thorough medical history of the patient before prescribing isotretinoin. This will help exclude patients with a pre-existing high risk of epistaxis, such patients can be prescribed other safer anti-acne treatments. It can guide appropriate patient selection for isotretinoin therapy and will facilitate better treatment compliance and outcomes.

We would also like to shed light on the smaller subgroup of patients in the study who experienced a more severe form of epistaxis. Nearly one-fourth of the study patients experienced epistaxis of moderate or second-degree severity and frequency, while another 8.6% patients had third degree frequency of epistaxis and a period of bleeding that ranged between 10-30 minutes. In our opinion, such patients should seek medical help from an ENT specialist. However, 93.5% patients in our study were not instructed by their dermatologists regarding the need for any ENT consultation. Seven patients in the study needed to be taken into the ER for management of their epistaxis. In this context, it is noteworthy that epistaxis accounts for 33% of all otolaryngology ER visits. Hence, having an ENT specialist in loop right from the beginning of isotretinoin therapy seems prudent. Two patients needed to undergo blood transfusion post-epistaxis, which is quite a rare finding as past evidence has shown a mere 0.2% hospitalization rate even for severe epistaxis.[18] These findings should serve as an alarm for dermatologists as isotretinoin use does have the potential to cause moderate-to-severe epistaxis in a smaller subgroup of patients. This again circles back to the need for proper patient education and simultaneous ENT consultation to enhance patient safety and outcomes, during isotretinoin therapy.

We strongly concur with the widely published thought lack of such patient education can increase treatment-related complications and compromise therapeutic outcomes. In the current study, close to two-thirds of the participants were not informed about the side effects of isotretinoin and preventive measures to be exercised for the same, by their prescribing dermatologists. The need to have at least one medical consultation from an ENT specialist while using oral isotretinoin seemed to be sweepingly neglected by the prescribing doctors. More than 50% participants were completely ignorant regarding the importance of nasal moisturization. In our view, the episodes of mild epistaxis could have been avoided and the more severe ones could have been minimized or reduced in intensity, had the prescribing dermatologists counseled their patients thoroughly regarding the nasal adverse effects of isotretinoin and steps to be taken to prevent epistaxis.[7,12,19]

Nasal mucociliary clearance (NMC) is a crucial defence mechanism which helps in elimination of pathogens and toxins from the nasal passages, by constant ciliary movement. However, previous evidence has demonstrated that isotretinoin tends to adversely impact NMC, thus prolonging the mucociliary clearance time (MCT), the time required for clearance of deleterious substances and pathogens from the nose, via ciliary action. This causes a water-electrolyte imbalance in the nasal mucosa, increases the viscosity of nasal mucus, eventually leading to nasal dryness and crusting.[9,12,20]

Study limitations. As we did not have histopathological evidence from the patients in our study, we could not elucidate the cellular changes seen in the nasal mucosa, with the use of isotretinoin. Also, a simple investigation like the saccharin test, which is commonly used to determine NMC and MCT, was not carried out on our study population. Hence, we cannot present any precise figures for impairment of MCC and delay in MCT, among isotretinoin users in our study. However, we concur with this pathogenesis of epistaxis and recommend future studies on this topic to incorporate histopathological data in their results. This could help in better understanding the cellular nuances associated with isotretinoin-induced epistaxis. Besides the lack of histopathological data, the study had a few other limitations too. This was a single-center study, with a limited sample size. We believe multicentric clinical studies with a larger sample size and a more diverse demography could provide more robust data on this subject.

In conclusion, the prevalence of isotretinoin-induced epistaxis is significantly high among Saudi patients. The complication can affect nearly half of the patients receiving this drug. Isotretinoin can cause >5-fold increase in epistaxis, as compared to baseline. Prior history of nasal bleeding can significantly escalate the risk of epistaxis during isotretinoin treatment. Nasal obstruction while using isotretinoin and poor awareness among patients regarding the risk of epistaxis and its preventive measures, also represent significant risk factors. Isotretinoin induced epistaxis is mostly mild and manageable; however, certain pre-existing disorders and ongoing medications can aggravate the condition. A small but clinically important subgroup of patients can experience a mild-to-severe form of isotretinoin-induced epistaxis. Isotretinoin should be prescribed judiciously by dermatologists, in consultation with ENT specialists, and with adequate patient education

regarding its potential nasal adverse effects and steps to mitigate the same. This study provides fresh evidence of isotretinoin-induced epistaxis in a Saudi cohort and highlights Saudi patients' poor awareness regarding this frequent complication of isotretinoin therapy. The study prompts ENT specialists and dermatologists in Saudi Arabia, to investigate isotretinoin-induced epistaxis, through larger and more robust studies in the future

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