INTRODUCTION

Oral isotretinoin has been in use since 1982, for “severe, nodulocystic acne, refractory to treatment, including oral antibiotics” and since 2000 with expanded indication to include acne which causes physical scarring and psychological impact. With this expanded recommendation, nearly 1.2 million prescriptions were...
captured from December 2005 to February 2011, through PLEDGE Registry in the US.\(^3\)

Even though the benefits outweigh the risks, isotretinoin has its share of side effects. Of all the side effects, three are significant and subject to much debate—depression and suicidal ideation,\(^3,4\) inflammatory bowel disease,\(^5\) and finally hypertrophic scar and keloid formation.\(^6\)

Of the above, the hypertrophic scar and keloid formation are the focus of this paper. The present established standard preoperative surgical care, so far advises the stoppage of oral isotretinoin 6–12 months before any dermatosurgery.\(^7\) This was based on the early reports of keloids or delayed wound healing, in patients on isotretinoin during surgery documented in 1980’s.\(^8,9\) Surprisingly, this recommendation stemmed from 9 cases reported from different authors.

However in 1985, Roenigk et al. had performed dermabrasion in nine patients on isotretinoin and reported normal “initial” skin healing.\(^10\) However, despite this observation, for nearly two decades, stopping oral isotretinoin before dermatosurgery was the medico-legal standard practice, unchallenged.

Between 2004 and 2012, a few case series and prospective studies were published documenting the safety of dermatosurgery and laser therapy in patients on oral isotretinoin. These included laser hair removal with diode laser,\(^11,12\) long-pulsed neodymium-doped yttrium aluminum garnet (Nd: YAG) laser,\(^13\) diamond fraise dermabrasion,\(^14\) and chemabrasion.\(^15\) The data are summarized in Table 1. However the studies were small and not significant enough to alter the recommended guideline, and larger studies were needed. The recommendation however put restrictions on physicians while performing procedures in these patients as it would have medicolegal implications and also often denied the right treatment to them.

In view of this, to establish proper evidence for a change in the guidelines and facilitate evidence-based practice, in 2012, the Association of Cutaneous Surgeons India, ACS (I) proposed to start a multicentric study to establish the safety of procedures in such patients. The study was named as per acronym ISO-AIMS study which stood for “Isotretinoin and Surgical Outcome: ACS (I) Multicentric Study.” 11 investigators from across India took part in the multicentric trial [Figure 1].

**MATERIALS AND METHODS**

The study was prospective, interventional, and nonblinded in nature. The scope of the study is shown in Table 2.

A total of 183 cases were enrolled across 11 centers. The age, sex, and Fitzpatrick skin types are shown in Table 3. The indications for oral isotretinoin are shown in Table 4. Of these patients, 61 had stopped oral isotretinoin intake before surgical intervention and 122 were taking concomitantly isotretinoin during surgical intervention. Dosage range was 2–110 mg/kg (180–9160 mg) [Table 5].

In the 183 cases, a total of 504 interventions were performed as shown in [Table 6]. The devices and parameters used are shown in Table 7. The data were statistically analyzed using descriptive statistics, contingency coefficient test, and Chi-square test.

Of the 183 cases, 82 cases (44.8%) were of skin type IV, and 72 cases (39.3%) were of skin type V. Furthermore, significant was 122 (66.66%) cases were on concomitant oral isotretinoin. The skin type, age group, and indication for isotretinoin had a significant \(P < 0.000\) except the gender distribution.

Of the interventions, chemical peel – 246 sessions (48.9%) – was the most common performed, followed by different lasers – 184 sessions (37.6%).

**RESULTS**

Two sets of adverse events were documented [Table 8]. Keloid formation was noted in 2 cases. The second set of adverse events was were transient like-erythema, pigmentation, acne, and hemorrhage. However, 93.8% cases did not have any adverse events.

Laser-diode/long-pulsed Nd: YAG or IPL-assisted hair reduction and acne therapy totaling 38 sessions had no adverse outcome. Salicylic acid peel performed in 30 sessions was without side effects. Microdermabrasion, 44 sessions was also safe. 8 skin biopsies also were safe. One wisdom tooth extraction healed well, despite patient
Table 1: Oral isotretinoin intake and scarring postintervention - review of literature

| Year of publication | Journal | Purpose of publication | Number of patients treated | Oral isotretinoin | Skin type | History of hypertrophic scar present | Duration of follow-up | Site of dermabrasion/laser | Pre- and post-operative complications | Limitations of study |
|---------------------|---------|------------------------|---------------------------|-------------------|-----------|--------------------------------------|-----------------------|---------------------------|---------------------------------------|---------------------|
| 1985[13] | J Dermatol Surg Oncol; 11:396-8 | Acne, retinoids, and dermabrasion on face | 9 | Concomitant isotretinoin | ? | 9 days | Rhinophyma | No complications | Case series |
| 1986[9] | J Am Acad Dermatol; 15 (2 Pt 1):280-5 | Patients on isotretinoin during dermabrasion started almost 4-14 months duration before intervention | 3 | ? | Yes | 1-3 months | Face | 1-3 months noted keloids on the face. Resolved in 2 patients with interventions | Case report |
| 1988[10] | Br J Dermatol; 118:703-6 | Delayed wound healing and keloid formation following argon laser therapy or dermabrasion | Patient1 Patient 2 Patient 3 | On isotretinoin concomitant oral isotretinoin Postprocedure oral isotretinoin | ? | 8 months | 6 months 2 months | Delayed postinflammatory scarring | Case report |
| 2004[12] | Dermatol Surg. 30:1205-7 | Diode hair reduction in patients on oral isotretinoin | 7 | Concomitant 63 mg/day isotretinoin mean of 4 months duration Concomitant | II-III | 1 month | Face, argon laser for rosacea Traumatic scar Rhinophyma dermbraded | One patient had blister, by week 1, which resolved | Case series |
| 2005[11] | Dermatol Surg. 31:380-1 | Diode hair reduction and oral isotretinoin | 6 | Concomitant | II-III | 4 years | Facial hair reduction | Erythema immediate, crusting which resolved in few days | Case series |
| 2009[10] | J Cosmet Laser Ther 2009;11:56-60 | Long-pulsed Nd: YAG laser reduction in patients taking oral isotretinoin, concomitantly | 11 | Concomitant, but stopped during the laser therapy day | III-V | 12 weeks postlaser | Face and extrafacial site hair reduction | No adverse events | Retrospective case series |
| 2010[14] | Dermatol Surg 2010;36:483-9 | Outcome of diamond fraise dermabrasion in patients taking oral isotretinoin | 7 | On the drug during intervention | I-V | Yes in one patient | 6 months postsurgery | Nil in all and even in the case with history of hypertrophic scarring | Interventional type. No control group |
| 2012[15] | Dermatol Surg 2012;38:1521-6 | Outcome after chemabrasion, in patients who had stopped isotretinoin | 10 | Stopped isotretinoin 3 months prior | II-V | Yes in 3 patients | 6 months postsurgery | No hypertrophic scarring | Interventional prospective study |

being on isotretinoin. The wisdom tooth extraction outcome in our study concurs with the currently documented experience in literature of 26 cases, which is safe.[16]

Of the other procedures carried out – in glycolic peel [Figure 2], of 147 cases, 6 had erythema. All had one coat of peel applied. One case on Refinity 70% buffered glycolic peel, had immediate erythema which started with in a minute, which was neutralized and resolved without sequelae (manufacturer recommended contact time 4–10 min). The second case of glycolic acid peel had erythema which resolved only with tacrolimus ointment 0.01% by 2 weeks. The third case had facial keloid formation at the site of glycolic acid application [Figure 3] and interestingly developed keloid later on truncal zone too (cumulative dose in this case - 2100 mg of isotretinoin). This was managed by intralesional steroids. In other procedures, 2 cases of combination peel developed erythema lasting for 5 days.

In the ablative fractional erbium-doped yttrium aluminum garnet (Er: YAG) series, one had postinflammatory
pigmentation, which resolved in 3 weeks. The second case of fractional Er: YAG laser had prolonged redness requiring topical steroids for 2 weeks. The third case in this intervention had a flare of acne treated with adapalene 0.1% gel night daily.

Interestingly, a case with acne vulgaris with a history of keloid on the trunk, who was on isotretinoin, did not develop keloid on the face when fractional Er: YAG laser was used to treat scar on the face [Figure 4].

Conventional ablative CO₂ laser resurfacing was done in 19 cases on face. Of these 14 cases developed post inflammatory hyperpigmentation, which resolved with sunscreen and hydroquinone by 3 months. However, none developed keloid or delayed wound healing.

The only microneedling case enrolled and subjected to 7 sessions of therapy had pigmentation which resolved.

A single case of acne vulgaris with nevus of Hori underwent 4 sessions with Q-switched Nd: YAG laser had erythema twice posttherapy which lasted for few minutes and resolved.

Subconjunctival hemorrhage post-LASIK surgery (laser-assisted in situ keratomileusis) in a case resolved without permanent sequelae. It is known that isotretinoin causes corneal xerosis, so does LASIK surgery. LASIK surgery is contraindicated during isotretinoin. A gap of 6 months has been advocated before surgery. Furthermore, post-LASIK, isotretinoin should not be prescribed for nearly 6 months.[7]
In this study, not only facial fractional resurfacing but also extrafacial fractional resurfacing was done. One case of Er:Yag fractional laser and one case of CO\(_2\) fractional resurfacing were done on trunk region without any side effects.

Radiofrequency ablation of compound nevi on the face was done, in a case, with a cumulative dose of 4000 mg of isotretinoin. This patient developed a keloid.

Two cases of keloid were documented, which amounted to 0.4% of side effects in 504 interventions, with a significant \(P\) value of 0.000.
DISCUSSION

Of interest, in this prospective interventional study – “102 Fractional Er: YAG laser resurfacing, 19 conventional full face CO₂ laser resurfacing, 19 Fractional CO₂ laser resurfacing, 8 skin biopsies;” had no keloid/hypertrophic scar formation or delayed healing. All the above were collagen-specific interventions.

Laser or IPL-assisted hair reduction, being performed in 38 sessions, being more melanin specific, had no keloid/hypertrophic scar formation.

Thirty sessions of salicylic acid peels, 65 sessions of combination peels had no keloid/hypertrophic scar formation. However, of 147 sessions of glycolic acid peel, one case developed keloid at the site of peel and distant site postprocedure. This event of distant site keloid could be idiosyncratic.

The second case of keloid on the face followed radiofrequency ablation of compound nevi.

However, there were minor reversible outcomes such as pigmentation, erythema, and acne. If one compares our study and literature, which could serve like control data, the occurrence of reversible events in isotretinoin group is comparable [Table 9].

In a recent retrospective study,[23] about 55 patients undergoing laser-assisted hair reduction and postacne scar reduction in patient taking oral isotretinoin; the authors found no keloid or hypertrophic scar or delayed wound healing.

CONCLUSION

This study with 504 interventions done in patients taking oral isotretinoin with – glycolic/salicylic/combination acid peels, fractional Er: YAG laser resurfacing/fractional CO₂ laser and conventional CO₂ laser resurfacing, microdermabrasion had a single documented keloid in glycolic peel group. This was probably idiosyncratic. The second case of keloid following radiofrequency ablation of compound nevi however could not be explained.

The results of this study, further enhance the already accumulating evidence, about the safety of procedures in patients receiving isotretinoin and further provide additional evidence that the current recommendations for avoiding procedures may not be valid and need revision.

Table 9: Comparison of adverse events in ISO-AIMS study and literature review

| Intervention                                  | Complication | Present study-ISO-AIMS study (with isotretinoin) (%) | Literature review (without isotretinoin) (%) |
|-----------------------------------------------|--------------|------------------------------------------------------|---------------------------------------------|
| Glycolic peel                                 | Erythema     | 4.08                                                 | 0 - Garg et al.[18]                         |
| Ablative fractional Er: YAG Laser             | Erythema     | 0.98                                                 | 0 - Manuskiatti et al.[19]                  |
| Conventional full face CO₂ resurfacing        | Acne         | 0.98                                                 | 2-10 - Metelitsa et al.[20]                 |
| Conventional full face CO₂ resurfacing        | Pigmentation | 73                                                   | 100 - Alster et al.[21]                     |

Er: YAG: Erbium-doped yttrium aluminum garnet

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. American Academy of Dermatology Position Statement on Isotretinon (Approved by the Board of Directors 9 December, 2000; Amended by the Board of Directors 25 March, 2003, 11 March, 2004, and 13 November, 2010). Available from: http://www.aad.org/Forms/Policies/Uploads/PS/PS-Isotretinoin.Pdf. [Last accessed on 2014 Jan 02].
2. Drug Safety and Risk Management Advisory Committee; Dermatologic and Ophthalmic Drugs Advisory Committee. Available from: http://www.fda.gov/Advisorycommittees/calendar/ucm275806.htm. [Last accessed on 2013 Dec 15].
3. Hazen PG, Carney JF, Walker AE, Stewart JJ. Depression – A side effect of 13-cis-retinoic acid therapy. J Am Acad Dermatol 1983;9:278-9.
4. Bigby M. Does isotretinoin increase the risk of depression? Arch Dermatol 2008;144:1197-9.
5. Godfrey K.M, James MF. Treatment of severe acne with isotretinoin in patients with inflammatory bowel disease. Br J Dermatol 1990;123:653-5.
6. Abdelmalek M, Spencer J. Retinoids and wound healing. Dermatol Surg 2006;32:1219-30.
7. Abdelmalek M, Spencer J. Retinoids and Wound Healing. Dermatol Surg 2006;32:1219-30.
8. Rubenstein R, Roenigk HH Jr., Stegman SJ, Hanke CW. Atypical keloids after dermabrasion of patients taking isotretinoin. J Am Acad Dermatol 1986;15(2 Pt 1):280-5.
9. Zachariae H. Delayed wound healing and keloid formation following argon laser treatment or dermabrasion during isotretinoin treatment. Br J Dermatol 1988;118:703-6.
10. Roenigk HH Jr., Pinski JB, Robinson JK, Hanke CW. Acne, retinoids, and dermabrasion. J Dermatol Surg Oncol 1985;11:396-8.
11. Khatri KA. Diode laser hair removal in patients undergoing isotretinoin therapy. Dermatol Surg 2004;30:1205-7.
12. Cassano N, Arpaia N, Vena GA. Diode laser hair removal and isotretinoin therapy. Dermatol Surg 2005;31:380-1.
13. Khatri KA. The safety of long-pulsed Nd: YAG laser hair removal in skin types III-V patients during concomitant isotretinoin therapy. J Cosmet Laser Ther 2009;11:56-60.
14. Bagatini E, dos Santos Guadanhim LR, Yarak S, Kamamoto CS, de Almeida FA. Dermabrasion for acne scars during treatment with oral isotretinoin. Dermatol Surg 2010;36:483-9.
15. Picosse FR, Yarak S, Cabral NC, Bagatini E. Early chemabrasion for acne scars after treatment with oral isotretinoin. Dermatol Surg 2012;38:1521-6.
16. Sharma J, Thiboutot DM, Zaenglein AL. The effects of isotretinoin on wisdom tooth extraction. J Am Acad Dermatol 2012;67:794-5.
17. Miles S, McGlathery W, Abernathie B. The importance of screening for laser-assisted in situ keratomileusis operation (LASIK) before prescribing isotretinoin. J Am Acad Dermatol 2006;54:180-1.
18. Garg VK, Sinha S, Sarkar R. Glycolic acid peels versus salicylic-mandelic acid peels in active acne vulgaris and post-acne scarring and hyperpigmentation: A comparative study. Dermatol Surg 2009;35:59-65.
19. Manuskiatti W, Iamphonrat T, Wanitphakdeedecha R, Eimpunth S. Comparison of fractional erbium-doped yttrium aluminum garnet and carbon dioxide lasers in resurfacing of atrophic acne scars in Asians. Dermatol Surg 2013;39 (1 Pt 1):111-20.
20. Metelitsa Al, Alster TS. Fractionated laser skin resurfacing treatment complications: A review. Dermatol Surg 2010;36:299-306.
21. Alster T, Hirsch R. Single-pass CO2 laser skin resurfacing of light and dark skin: Extended experience with 52 patients. J Cosmet Laser Ther 2003;5:39-42.
22. Chandrashekar BS, Varsha DV, Vasanth V, Jagadish P, Madura C, Rajashekar ML. Safety of performing invasive acne scar treatment and laser hair removal in patients on oral isotretinoin: A retrospective study of 110 patients. Int J Dermatol 2014;53:1281-5.
APPENDIX 1

(Abridged version)

Demographic data

Name: ____________________________  Age: ________  Sex: ________

Patient identification number (hospital registration number): ____________________

Address: __________________________________________________________________________________________

___________________________________________________________________________________________________

Contact phone numbers: ________________________  E-mail id if present: _________________________________

Occupation: _____________________  Patients skin Fitzpatrick type: __________________________

ACS (I) reporting code:_______________________________

Indication for oral isotretinoin (kindly tick the indication)

1. Acne vulgaris
2. Acne rosacea
3. Other indications ________ (kindly write)

Table 1: Isotretinoin current dosage, duration, and frequency (kindly fill the data in detail)

| Date | Dosage | Daily | Intermittent |
|------|--------|-------|--------------|

Table 2: Isotretinoin, past dosage, and duration since stopping

| Date of stopping isotretinoin | Duration after stopping the drug | Dosage administered cumulative dose |
|-------------------------------|----------------------------------|-------------------------------------|

Relevant patient history

History of keloids/hypertrophic scars_______ (yes/no)

Procedures indications

1. Acne scar- atrophic/ hypertrophic
2. Postacne macules - hyperpigmentation
3. Hair reduction
4. Scars - posttraumatic, chicken pox
5. Excision of scars/biopsy
## Procedure performed

### Chemical peel

**Agent used (write the ingredients, concentration, pH, buffered or not)**

- Glycolic acid
- TCA
- Salicylic acid
- Combination

| Date | Time of contact | Site of peel-face, back, upperlimbs | Immediate side effects* (within 3 days) | Delayed side effects | Time of resolution of complications, and how it was managed |
|------|----------------|-----------------------------------|----------------------------------------|---------------------|----------------------------------------------------------|

### Hair reduction - laser assisted

**Device – Long-pulsed Nd:YAG, diode laser, IPL, diode with radiofrequency, IPL with radiofrequency**

| Date | Site-face, trunk, limbs | Spot size | Pulse duration | Fluence | Cooling system | Immediate complications | Delayed complication | Time of resolution of complications and how it was managed |
|------|-------------------------|-----------|----------------|---------|---------------|------------------------|---------------------|----------------------------------------------------------|

### Fractional - ablative/nonablative

**Indications - acne scarring, photoaging, rejuvenation**

**Device - Wavelength: __________, Laser source - Er:YAG, CO2, Er:glass, diode, Nd:YAG**

| Date | Site of therapy | Spot size/pixel size | Fluence/Energy | Pulse duration | Pixel density | Immediate complications | Delayed complications | Time of resolution of complications and how it was managed |
|------|----------------|----------------------|----------------|----------------|---------------|------------------------|-----------------------|----------------------------------------------------------|