Intralesional excision as a surgical strategy to manage keloid scars: what’s the evidence?

Ioannis Goutos

Abstract

Introduction: Keloid scars are a particularly challenging clinical entity and a variety of management approaches have been described in the literature including intralesional surgery. The current literature lacks a summative review to ascertain the evidence base behind this surgical approach.

Methods: A comprehensive English literature database search was performed using PubMed Medline, EMBASE and Web of Science from their individual dates of inception to March 2018. We present the different rationales proposed for the use of this technique, the clinical outcomes reported in the literature as well as the scientific basis for intralesional excision of keloid scars.

Discussion: A number of arguments have been proposed to support intralesional excision including avoiding injury to neighbouring non-keloidal skin and the deep layer of the dermis, removal of the most proliferative fibroblastic group as well as debulking to facilitate the administration of injectable steroid. The most current literature does not provide sufficient support for the adoption of intralesional excisions based on data emerging from basic science as well as clinical outcome studies.

Conclusion: Emerging evidence supports the extralesional excision of keloid scars based on current mechano-biological, histological as well as clinical outcome data. Further trials comparing extralesional and intralesional surgical practices are eagerly awaited to ascertain the role of intralesional excisions in the keloid management arena.

Keywords

Intralesional, intramarginal, scar, keloid, hypertrophic, extralesional

Lay Summary

Keloid scars are a particularly challenging subset of scars to treat successfully. Complete (extralesional) removal and radiotherapy represent one of the most efficacious combined modalities for treatment; nevertheless, a number of scar services offer the option of partial (intralesional) removal for keloid scars frequently in conjunction with steroid therapy. This study was undertaken to find out how effective partial removal of keloids is in clinical practice. Based on the available literature, there is limited evidence that this approach can provide reliable long-term results; emerging data on the scar forming activity of different parts of keloids as well as mechanical factors contributing towards keloid growth fail to support partial scar removal techniques for this subset of scars.

Introduction

Keloid scars represent a challenging clinical entity, whose pathophysiology is thought to involve an impaired balance between fibroblastic

Corresponding author:
Ioannis Goutos, Centre for Cutaneous Research, Blizard Institute, 4 Newark Street, London E1 2AT, UK.
Email: i.goutos@qmul.ac.uk
proliferation and apoptosis\textsuperscript{1} as well as possible endothelial dysfunction.\textsuperscript{2,3} Historically, hypertrophic and keloid scars have been considered as separate clinical and histological entities; nevertheless, recent work suggests that they are contiguous scar subtypes with keloids representing the severe end of hypertrophy by virtue of a more prolonged and intense inflammatory activity within the dermis.\textsuperscript{3,4}

Management options can be divided into those aiming to:

1. decrease the bulk of the scar and improve symptoms—most commonly pain and itch; modalities in this category include intralesional steroid administration and cryosurgery;\textsuperscript{5–7} or
2. replace the bulky keloidal mass with a fine and symptom-free surgical scar. Some historical literature reports suggest that isolated extralesional excision of keloid scars is associated with a very high rate of recurrence of up to 80–100%;\textsuperscript{8} nevertheless, the addition of postoperative radiotherapy yields a significantly lower rate of recurrence in the range of 2–33%, raising the role of adjuvant radiotherapy in achieving favourable long-term results.\textsuperscript{9}

A number of specialist services offer the option of intralesional (or intramarginal) excision of keloid scars. This can be defined as a partial excision technique using incisions within the peripheral borders of the existing scar to a variable deep clearance and wound closure via approximation of the remaining keloidal rims. The aim of this work is to explore the theoretical basis/rationale for intralesional excision as presented by various authors over the last decades, delineate the different modifications of pertinent surgical techniques and appraise the level of evidence relating to outcomes following this technique.

**Methodology**

A comprehensive English literature database search was performed of PubMed Medline, EMBASE and Web of Science from their individual dates of inception to March 2018 using the following keywords: keloid AND intralesional OR intramarginal AND excision. The retrieved abstracts were screened for relevance to the field of study and filtered according to the inclusion criteria, which included original research, case series/reports and review articles elaborating on the philosophy, basic science evidence and outcomes of intralesional excision. Reports were excluded if the surgical technique involved the use of a keloidal fillet/rind flaps or the exclusive use of split skin grafting for wound coverage. We limited our search to human studies only and excluded letters, meeting abstracts, proceedings reports, editorial material and notes.

**Results**

A total of 638 abstracts were identified in the original search (95 in PubMed Medline, 211 in EMBASE and 332 in Web of Science). The abstracts were screened for relevance and full texts were read in full to confirm eligibility for inclusion into the work. This exhaustive literature search identified four reports describing different intralesional excision techniques, another four elaborating on the philosophy behind this surgical technique and six providing data on outcomes following intralesional excision for keloid scars.

**Different rationales proposed in favour of intralesional excision**

A number of different rationales have been proposed in the literature to support the intralesional excision of keloids as a surgical strategy:

1. Avoidance of incision placement in neighbouring ‘keloid prone’ skin. The high rate of recurrence following extralesional excision without adjuvant radiotherapy has been linked to inducing injury to the skin immediately adjacent to the keloid mass.\textsuperscript{9} This forms one of the supporting rationales for the intralesional method, which removes the bulk of the scar by staying within the keloidal confines.\textsuperscript{10}

2. Prevention against injury to the deep portion of the dermis within the keloid. Another supporting argument relates to the fact that a subset of intralesional excisions is performed in a manner which avoids injury to the deepest layer of the dermis (i.e. exposing no fat during the procedure). Violation of this layer of the dermis has been postulated to signal the production of excess collagen synthesis in keloid scars.\textsuperscript{11}

3. Removal of the most proliferative fibroblast group within the scar. More
specifically, it has been proposed that keloidal fibroblasts within the centre of the lesion have lower levels of apoptosis compared to superficial and deep portions. Therefore, removal of the central portion of a keloid predisposes to lower levels of recurrence by leaving behind cells more likely to undergo programmed cell death.1

(4) Mechanical debulking. Some authors have proposed intralesional excision of keloids as a means of decreasing the bulk of keloid scars with a view to facilitating postoperative intralesional steroid injections. Given that courses of steroid injections are prolonged and associated with discomfort, especially in longstanding, bulky non-compliant scars, the strategy translates into an overall reduction in the number of adjuvant injections needed and minimisation of discomfort as well as topical side effects.10

(5) Protective action of the keloidal rim against tensile forces. It has been advocated that the perimetrical rim of tissue left behind in the intralesional technique is able to act as a physical restraining splint. This has been postulated to eliminate the aggravating effect of physical tension on excessive collagen synthesis, which is central to keloidal pathophysiology.12

Intralesional excision techniques

A wide variety of techniques have been described for the intralesional excision of keloid scars relating to the management of both peripheral as well as deep margins.

- Straatsma described excision of the central portion of the scar leaving 1/8th inch (i.e. approximately 3 mm) of its external border to allow bulk reduction and eliminate invasion of ‘normal’ surrounding tissues.15
- Conway advocated excision within the pathological tissue borders in a bevelled manner allowing the formation of a three-dimensional phalanx of keloid. He also stressed the importance of avoiding the involvement of healthy skin in wound closure.14
- Kitlowski advocated an incision, which leaves sufficient peripheral margins for closure without the necessity of suturing normal skin, while the depth of the keloid is excised into normal fat. Furthermore, he proposed that the margins of the scar are ‘undercut’ to relieve tension before layered closure occurs leaving a narrower and flatter keloid lesion.15
- Peracok proposed an excision technique, which leaves a small (< 1 mm) rim of scar and the deep margin does not expose any subcutaneous fat.11

Outcomes following intralesional excision of keloid scars

A small number of studies have been identified providing outcome data following intralesional excision in combination with a variety of adjuncts including steroids and radiotherapy for keloid scars.

In 1960, Conway et al. published a comparative study of results obtained with the following three different regimens for a cohort of 154 patients with keloid scars followed up for a period between six months and six years:

1. intralesional excision and direct closure with 32-gauge stainless-steel wire or tie-over skin graft (28 patients);
2. intralesional excision with adjuvant X-ray therapy (24 patients);
3. intralesional excision and cortisone derivative injection for three weeks postoperatively (59 patients); and
4. the combination of all three modalities: intralesional excision; X-ray therapy; and steroids (43 patients).

Intralesional excision was performed within the confines of the scar leaving a narrow margin at the junction of keloid and normal skin and not exposing fat at the depths of the dissection. In the first cohort of 28 cases treated with intralesional excision, six patients were lost to follow-up and the rate of recurrence was 45% (the differential rate between direct closure and split skin grafting was unfortunately not specified). Out of the 59 patients treated with intralesional excision and cortisone derivative injection, primary closure was performed in 48 patients with a rate of recurrence of 23% (the corresponding rate in the skin graft group of 11 patients was 55%).14

Another North American report in 1967 described intralesional excision in the context of managing a recurrent auricular keloid combined with the postoperative use of intralesional steroid. The exact technique comprised reduction of the
 keloidal bulk, and thinning down of the resulting flaps leaving behind a thin layer of ‘rubbery tissue’ on the wound background. The steroid regimen comprised the use of 25 mg of 10 mg/mL triamcinolone on day 9, followed by 30 mg the following day and repeat administration at 1–3 weekly intervals for a total of 21 injections. No evidence of recurrence was reported in this report, which had a follow-up period of nine months.16

In a Zambian cohort published in 1980, 35 earlobe keloids were treated with intraleisional excision, closure and postoperative hydrocortisone (100 mg mixed with 1 mL of 2% xylocaine) every fortnight for an overall number of 6–10 injections. The exact surgical technique was not specified in this report and one immediate recurrence (rate of 2.85%) was seen at follow-up ranging between 6 to 12 months.17

Tang proposed the combination of intraleisional excision and lateral undermining to minimise tension in a cohort of three hypertrophic and eight keloid scars. Following full thickness excision just within the margins of the lesion, an injection of 10–30 mg triamcinolone around the margins was performed before closure. Repeated injections were performed weekly for a period of five months. Results among eight keloid scars showed two recurrences (overall rate of 25%) at a mean follow-up of 15 months (range for the whole cohort, which included three hypertrophic scars was 12–36 months).18

In another report published in 2007, 18 patients with head and neck keloids were treated with intraleisonal excision defined as the excision of the central bulk leaving behind a thin rim of peripheral keloid. The wound edges were undermined to permit advancement and primary closure was achieved. Adjuvant 40 mg triamcinolone injection was administered first at 10–14 days (i.e. time of suture removal) and an additional two at monthly intervals into the remaining lesion. The rate of recurrence in this study was 6%; the complications included wound dehiscence on postoperative day 3 (this was successfully re-sutured but lost to follow-up) and hypopigmentation in all patients.10

All the above studies have severe limitations including the small number of patients assessed, the lack of histological definition of keloid pathology and recurrence as well as the variable use of steroid dosage in the postoperative management; nevertheless, based on this summative literature review, the median rate of recurrence for intraleisional excision and adjunctive radiotherapy or steroids is 25%. It becomes clear that it is very challenging to assess the true rate of recurrence for isolated intraleisional recurrence for keloid scars, since only one study employed it as a sole modality giving a rate of recurrence of 45% for the subcohort, including direct and skin graft closure;14 these studies did not explore the comparison between intra- and extraleisonal modalities. It is therefore interesting to consider the findings of the following three reports.

One UK retrospective report investigated the influence of surgical excision margins on recurrence in 75 patients presenting with keloids in a variety of bodily locations including head and neck, chest and limbs undergoing either extra- or intraleisonal excision. All patients underwent adjuvant therapy including (compression, intraleisional steroid injections, silicone, radiotherapy) and recurrence was defined as a further raised scar following complete excision or in the cases of intraleisonal method, an increase in the visible scar mass. Furthermore, all keloids were histologically confirmed and their subtype was classified as either circumscribed (clearly demarcated borders) or infiltrative (borders not easily definable). Results suggest that there is a statistically significant difference in favour of extraleisonal excision at 3, 6 and 12 months (8.7% vs. 38.5%, 9.1% vs. 58.5% and 19% vs. 76.2%, respectively; P < 0.001) for both peripheral and deep margins. Furthermore, histological infiltrative borders and incomplete excision were strongly correlated (P < 0.001); a similar trend was identified based on clinically indistinct surroundings and excision completeness (P < 0.05).19

Two comparative studies between intra- and extraleisonal excision are available for hypertrophic scars. The first involved a retrospective review of 50 burn scars. The authors claimed to have obtained better results with intramarginal excision; however, this conclusion was not confirmed in the statistical analysis due to either a P value > 0.01 in the head and neck scar subcohort and the low number of patients recruited in the other subcohorts resulting in an overall low-powered study. Additionally, the outcome measures employed comprised a subjective improvement as a consensus of opinion without any objective criteria for recurrence been used.20

A different retrospective study compared the intraleisonal versus extraleisonal excision of 15 lower limb hypertrophic scars and skin graft coverage. The intraleisonal method involved leaving a scar border of 2 mm and the extraleisonal involved a peripheral clearance of 3–5 mm; results revealed a statistically significant difference in favour of the extraleisonal method (100% vs. 33% rate of recurrence; P = 0.011). This study had an immunohistochemical component, which
showed that transforming growth factor (TGF)-beta1 expression extends beyond the clinical margins of the hypertrophic scar; in addition, the expression of PCNA (proliferating cell nuclear antigen-marker of proliferating cells) was increased in this region compared to normal dermis, accounting for the increased recurrence rate for intramarginal excision. These findings point towards an infiltrative proliferating margin with tumour-like behaviour left behind following intramarginal excision. These conclusions are corroborative with the clinical study by Tan and assume significance given the recognition that keloids scars represent the extreme spectrum of scar hypertrophy.

Avoidance of incision to adjacent unscarred keloid prone skin

This rationale ‘proposed by’ Donkor does not fit with recent advances in the understanding of keloidal pathophysiology. Based on current mechanobiology theories, it is now widely recognised that one of the major predisposing factors for the genesis of keloids is tension on the dermis from the underlying musculature. This explains the high preponderance of certain sites, including the presternal, shoulder/upper back and suprapubic area, towards keloid scar formation as well as the shape of keloid scars, which are dictated by the underlying pull of the musculature. It is difficult to imagine why neighbouring skin would have a particularly different tension profile compared to keloidal lesion to make this argument valid from the index a mechanobiology perspective. The study findings by Tan linking recurrence with incomplete excision for peripheral (as well as deep) margins provide supporting evidence against the intralesional excision rationale.

Prevention against injury to the deep portion of the dermis

This proposed rationale is theoretically applicable to surgical intralesional techniques preserving the deeper layer of dermis as part of the keloidal resection. Recent work investigating the histopathological structure in auricular keloids has identified that three distinctive parts exist, whose central core contains abundant proliferation of abnormal blood vessels, increased inflammatory cell infiltration and high cellularity of activated young fibroblasts; this has been postulated to be a key portion for keloidal growth and recurrence. In other words, preservation of the deep layer of the dermis leaves behind a histologically active segment of the scar.

A clinical prospective study provides further support to the central proliferative core being a key part of keloid recurrence; this study investigated parameters inherent to auricular keloidal recurrence in 71 patients with an average follow-up of 19.8 months (range = 1.2–48.8 months). Results suggest that complete excision of the proliferating core in the deepest portion of auricular keloids is paramount for completeness of excision with a positive margin status shown to be associated with lesion recurrence ($P < 0.0001$). This work would support a more aggressive depth of excision and refutes the rationale for a big proportion of keloidal intralesional excision practices.

Removal of the most proliferative fibroblast group

Exploration of the literature on the differential activity of keloidal fibroblasts reveals interesting findings. A number of in vitro studies were identified in the literature search as below:

- Luo et al. studied the activity of keloidal fibroblasts in a culture model and compared apoptotic activity in superficial, central and basal portions of cultured cells deriving from intramarginal excision of six scars. The fibroblasts obtained from the superficial and basal regions of the keloidal tissue showed population doubling times and saturation densities similar to age-matched fibroblasts; cells from the centre of the keloid lesions nevertheless had significantly reduced doubling times and reached higher cell densities ($P < 0.001$).
- Supp et al. in an in vivo athymic mouse model showed that the expression of certain genes including type 1 collagen alpha 1 and transforming growth factor beta 1 was elevated in deep keloidal fibroblasts compared to superficial
(adjacent to the epidermis) and normal fibroblasts; the authors proposed that deep dermal fibroblasts secrete extracellular matrix causing thickening of the lower dermis and fibroblasts in the upper dermis spread along a longitudinal direction resulting in the typical bulging keloidal phenotype; the exact phenotype varying in different individuals based on the relative contributions of deep and superficial fibroblasts.\textsuperscript{24}

The findings of the above two studies could support the notion that excision of the central portion of a keloidal lesion removes the most proliferative population of fibroblasts, and provide the theoretical basis for intralesional excision provided the deep portion of the keloid is excised.

- Syed et al. investigated collagen I and III expression in keloidal fibroblast cultures deriving from the following sites: extralesional (macroscopically normal skin not involving the keloid), intraleSIONAL (top, middle and deep part of the keloid) and perilesional (growing margin of the keloid periphery). Expression levels of collagen types I and III were significantly higher in perilesional fibroblasts compared to extralesional and intralesional keloid biopsy sites, reinforcing the notion of a peripheral growing front in keloidal structure ($P < 0.05$).\textsuperscript{25} This would not support intralesional excision practices by virtue of leaving behind the comparatively most active fibroblastic group within the keloidal field.

- Seifert et al. employed gene microarrays to identify the differential gene expression within keloidal lesions and identified localised overexpression of the novel apoptosis inhibitor AVEN as well as invasion promoting genes such as PTHrP at the active peripheral margin; most interestingly, apoptosis-inducing genes such as ADAM12 and those inducing extracellular matrix degradation such as metalloprotease-19 are upregulated in the regressing keloidal centre.\textsuperscript{26}

- Javad et al. investigated the protein extract profiles of different regions in keloid scars using comparative proteomics analysis. They identified the expression of mitochondrial-associated proteins including adenosine-5-triphosphate subunit alpha (ATPA), creatine kinase (KCRM), glutathione S-transferase major (GSTP1) and sulfotransferase (ST1C2) at the keloidal margin suggesting an epicentre within the scar in terms of proliferative activity.\textsuperscript{27}

Limitations of the abovementioned studies include their in vitro nature as well as the lack of histological and clinical analyses linking differential fibroblastic activity with risk of recurrence. Nevertheless, summative appraisal of the findings on the differential activity of keloidal fibroblasts provides equivocal evidence supporting an intralesional approach, especially if it involves preservation of the deep layer of the dermis. More specifically, two studies support the rationale that the central part of keloids represents the less apoptotic and more metabolically active/fibrogenic site\textsuperscript{1,24} and one suggests the peripheral, actively growing front being key to keloidogenesis.\textsuperscript{25}

It is prudent at this point to investigate findings from keloidal studies using histological parameters as opposed to in vitro studies to further elucidate into the differential activity of fibroblasts.

- Initial work focusing on the histopathological appearance of keloid scars demonstrated a relatively acellular central core in the deepest portion of the lesion and a periphery of hyperproliferating fibroblasts.\textsuperscript{28} This reinforces the peripheral parts of keloidal lesions as key to progression based on fibroblastic activity alone.

- A very recent experimental study investigated the histological zones of 19 keloidal lesions from a variety of bodily sites. The superficial dermis layer comprised parallelly organised collagen fibres and spindle-shaped fibroblasts with an overall appearance similar to granulation tissue. The mid-dermal layer was thicker with compact collagen fibres and the most prominent fibroblast infiltration, whose cellular appearance suggest a static cellular state. The deep dermis was characterised by prominent degeneration and loosely organised hyalinised collagen. Comparison of superficial to deep layers revealed, that the number of fibroblasts decreased and were transformed from an active to a static state. Most interestingly, two sites were found to have prominent lymphocytic infiltration, namely the
perivascular area of the superficial dermis and the skin at the junction of keloid and healthy skin. Additionally, the most superficial dermal fibroblasts had the greatest migratory capacity in comparison to fibroblasts in normal skin and hypertrophic scars suggesting that the superficial dermis may play a key role in initiating keloid formation. This study shifts the paradigm of keloidogenesis away from the key role of deep fibroblasts to the superficial part of the lesion and reinforces the role of immune activation at the peripheral margins in the pathogenesis of keloid scars.

In other words, an intralesional excision irrespective of preserving the deepest layer of dermis intact or not, leaves behind a rim of peripheral and superficial active fibroblasts, which would promote a high rate of recurrence in cytological terms. The complexity of keloidogenesis clearly needs to be further elucidated with regards to differential fibroblastic activity.

Debulking

Other authors have viewed intralesional excision as a means of allowing the formation of less bulky keloid scar in order to facilitate postoperative intralesional steroid injections; the latter translates into the reduction of the number of adjuvant injections needed and minimisation of topical steroid side effects. There are no studies to substantiate this; nevertheless, it carries some gravity as a practical way of facilitating steroid delivery to large keloid scars.

Potential protective action of keloidal rim against tension

It has been advocated that an intramarginal scar excision leaves a perimetrical rim of tissue, which acts as a physical restraining splint; this has been postulated to eliminate the aggravating effect of physical tension on excessive collagen synthesis. Nevertheless, empirical personal experience would reinforce the published observation made by Minkowitz that, despite thinning of peripheral keloidal flaps, it is difficult to produce compliant enough scar edges to fold down and cover the resulting defect without tension.

Discussion

Keloid scars represent a challenging clinical entity in reconstructive practice and a number of contributing factors have been identified towards their pathophysiological development including:

1. genetic single nucleotide polymorphisms;
2. local mechanical tensile forces;
3. hormonal states associated with raised sex hormones (e.g. pregnancy, adolescence);
4. systemic inflammatory disorders including Castleman disease as well as hypertension.

Some basic tenets of optimal surgical practice for keloid scars relate to the relief of tension on the healing dermis and a variety of techniques have been described to this effect. These include the extralesional excision of the lesion to deep dissection planes and the placement of sutures in the deep as well as superficial fascial planes to allow approximation of the dermis with minimal tension; furthermore, the importance of further distributing intradermal tension with the use of Z-plasties is emerging in the literature. The adoption of postoperative adjuncts appears to be critical in obtaining favourable long-term results and radiotherapy represents the most efficacious modality associated with the lowest rate of recurrence; our literature search identified that steroids are the most popular adjunct following the intralesional excision of keloids.

The number of studies available in the literature focusing on outcomes following intralesional excision is very limited and are characterised by low evidence level (uncontrolled or retrospective) and provide a combined median recurrence rate of 25%. The only comparative study available appraising outcomes following intralesional versus extralesional keloidectomy practices points towards a statistically significant difference in favour of extralesional excision at the follow-ups at 3, 6 and 12 months ($P \leq 0.001$) for both peripheral and deep margin clearance.

A number of rationales proposed for an intralesional approach include preservation of
the integrity of perilesional ‘keloid prone’ skin and the deep portion of the dermis, the removal of the most proliferative fibroblastic group as well as mechanical debulking among others.

Review of the latest hypotheses based on mechanobiology would not support the rationale behind neighbouring skin to the keloidal lesion being keloid prone. Furthermore, there is strong emerging evidence that the incomplete peripheral clearance of keloids is associated with higher rates of recurrence with the rim of keloid left behind displaying an infiltrative tumour-like behaviour. The philosophy of not violating the deep portion of the dermis by performing a superficial intralesional clearance appears unfounded based on a study of keloids is associated with higher rates of recurrence based on a study of perilesional ‘keloid prone’ skin. This section has been shown to be associated with keloid recurrence in a statistically significant manner.

The data regarding which portion of keloid scars contains the most proliferative fibroblastic group (the removal of which would render the procedure more successful in minimising recurrence) are, to a certain extent, conflicting. Two in vitro studies point towards the deep portion containing less apoptotic and more actively fibrogenic fibroblasts and hence could support an intralesional excision provided it is performed to an adequate depth, most likely down to fat. The most current trend in proteomics and histological fibroblastic activity focuses on the comparatively higher metabolic activity of peripheral sites compared to intra- and extralesional sites as well as the potential key role of highly migratory superficial fibroblasts in keloideogenesis. These current trends would not support an intralesional approach irrespective of clearance depth given the preservation of superficial fibroblasts in the approximated lesional rims. The philosophy of intralesional excision acting as a pure debulking procedure carries some gravity, which needs to be weighed against the emerging evidence supporting an extralesional approach.

Conclusion
In conclusion, there is currently insufficient evidence to favour intralesional excision of keloids in favour of other techniques; rates of recurrence remain high from most isolated excisional techniques as well as those with ancillary techniques. Future randomised trials of similar scar and patient groups that take into account confounding factors including adjuvant interventions may elucidate optimal surgical strategies further.

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ORCID iD
Ioannis Goutos https://orcid.org/0000-0001-5853-6770

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