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Androgen Receptors and Keloid Treatment in Children: Insights on Androgen Insensitivity Syndrome

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ABSTRACT

Background: Keloids can form from an overgrowth of skin fibroblasts where the scar tissue extends beyond the initial boundaries of the injury; they are benign lesions. Studies indicated that androgens could influence these fibroblasts to cause excessive collagen deposition causing keloid formation (1). We aim to look at surgical and non-surgical management of keloids in children and to explore pain management during keloid treatment in children.

Methods: A systematic search was conducted using Medline, Embase, PubMed and Cochrane Library looking into the different keloid treatments used in children. As there were limited studies looking into pain management in children, an exclusion was made to investigate adult (age>18 years) studies. We hypothesized that the use of surgical and adjuvant therapy is better for steroid treatment.

Results: Out of the 33 abstracts, 21 articles fit the inclusion criteria.

Conclusion: Non-surgical treatments such as intralesional triamcinolone acetonide (TCA) and Botulinum toxin Type A reduced the volume of keloids up to around 80%. A combination therapy is safer with fewer side effects in the paediatric population. A study has also suggested the use of anti-androgenic treatment such as Finasteride or Combined Oral Contraceptives can help to reduce inflammation within the skin and provide 'long-term' health benefits to those predisposed to keloids. Surgical and non- surgical treatment

(including anti-androgenic treatment) may be used in those who develop keloids after

gender affirming surgeries in those with conditions such as Androgen Insensitivity Syndrome (2). Further studies are required to understand the multimodal therapy that can be used to treat keloids in children.

Keywords: keloid, steroid, corticosteroid, botulinum toxin type A, Androgen Insensitivity Syndrome.

1. INTRODUCTION

Keloids extend beyond the initial boundaries of the injury due to an overgrowth of skin fibroblasts. They appear elevated and are also associated with pain, itching as well as psychological stress (3). Even though the exact pathophysiology is still uncertain, keloid formation is likely to be related to the imbalance of fibroblast collagen synthesis and the proliferation and migration of keratinocytes (4). Some studies have also shown that there is an increase in TGF-B that leads to an abnormal response of fibroblasts causing keloids (5). Some of the most common causes of keloids include burn injuries, acne scars, previous surgery, varicella lesions or vaccinations (6). There seems to be a strong link between the increased susceptibility of keloids and genetics as they are common in black ethnic group but less common those from Far East, Southeast Asia or Indian subcontinent and rare in Europeans or white Americans. Keloids also occur more frequently in sites that are frequently stretched by daily movements such as the anterior chest, scapula and the lower abdomen (7).

Keloids remain very hard to treat due to their high level of recurrence and no clear management plan advised for both adults and children. The treatment modalities advised include surgical excision, corticosteroids, botulinum toxin Type A, radiotherapy or compression therapy (7). Many of these therapies are involved in inhibiting the inflammatory processes and pathological proliferation of fibroblasts that leads to keloid formation (3, 8).

Many studies recommend the use of multiple therapies to treat keloids however, there was no significant difference seen between monotherapy vs adjuvant combination whilst treating keloids (9).

Even though there have been many retrospective studies looking at keloid treatments in adults, there remains limited evidence on clinical trials looking into the effective management of keloids in children. Therefore, we aimed to perform a systematic review of surgical and non-surgical treatments used to treat keloids in children. We also aimed to identify different pain management used in keloid treatments (10).

2. METHODOLOGY

The clinical questions that were determined as follows

1. What are the available treatment modalities used to treat keloids in children? Look at the effectiveness of surgical and non-surgical management of keloids.

2. What is the peri-interventional management for pain in children undergoing keloid treatment?

The systematic review of the related literature published in the last 20 years were searched using MEDLINE, EMBASE, Cochrane Library as well as PubMed. The English translations for foreign studies were also included in this review.

The criteria for possible inclusion were as follows:

1. Patients age group 0-18 years

2. Surgical or non-surgical management for keloids

3. Pain management used in keloid treatments in children.

The exclusion criteria were as follows:

1) Patient's age group >18 years.

The following search terms were used during for our systemic review:

Keloid* OR keloid adj3 treat* AND "in children" AND surg* OR surg* adj3 treat* OR botox OR "botulinum toxin" OR "androgen receptors".

When looking at per-operative pain relief in keloid treatment, we also added the search terms "pain relief" OR "pain adj3 manage*" AND child*

There were limited articles that looked into pain management for keloid treatment in children. This could be because there may be a lack of tools that enable us to accurately measure pain experienced in children objectively or subjectively. Therefore, an exclusion was made to look into pain management for keloid treatments in adults (age>18 years).

The studies were then collated mentioning the year, type of study, the number of patients involved and their mean age. Any duplicates of the study were also noted and excluded during the collection. The quality of evidence of the studies included in the systematic review was not evaluated. Most of the studies we have selected include a small sample size that ranges form 5 - 607 patients in the studies. The main types of studies included in this review include randomized controlled trials and some case reports. Further details of the study have been outlines in the *Table 1*.

3. RESULTS

There was a total of 33 abstracts that were identified mentioning keloid treatment and pain management in children. This also included the abstracts that mentioned pain management in keloid treatment for adults. After all the abstracts were screened, a total of 14 abstracts were chosen as the others were either irrelevant or they matched the exclusion criteria. (*Figure 1*)

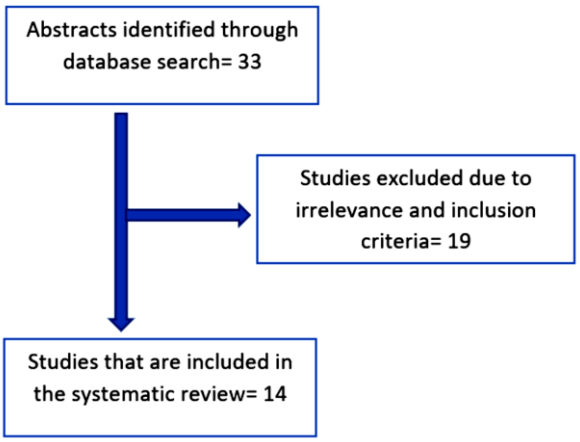

Figure 1. Outline of the selection process for the articles used in this systematic review.

The full list of the studies used in this systematic review is outlined in *Table 1*. From the list of papers identified, the authors have read and collated data about the different types of treatments used for keloids and their effectiveness in reducing the size of the keloid. We also analysed the different types of pain management whilst having keloid treatments and their effects considering the reported Visual Analogue Scale (VAS) during the studies.

Study	Year	Type	Number of patients	Mean age	Procedure	Outcome
(Acosta et al. 2016)	2016	Prospective clinical trial	21	12 years (6-14 yrs)	Intralesional triamcinolone acetonide (TAC)	82.7% size reduction of keloids
(Park and Chang 2015)	2015	Retrospective	203	15 years (12-18 yrs)	Surgical excision, intralesional steroid injections and pressure therapy	88.6% successful treatment with 11.4% recurrence
(Ogawa et al. 2009)	2009	Systematic review	5	NA	Radiotherapy	Risk of carcinogenesis from radiotherapy is very low
(Bonnardeaux and McCuaig 2020)	2020	Retrospective	21	2-15 yrs	Multimodal therapy: surgical excision, CO2 laser therapy, TAC injections, silicone and pressure devices	82.4% of complete clearance
(Bourdier et al. 2021)	2021	Randomised controlled trial	607	18 months- 6 years	Vibration vs mixture of local anaesthetics (EMLA patch) during cannulation in children	Vibration not as effective as EMLA patch
(Secil et al. 2014)	2014	Randomised controlled trial	60	2- 24 months	Vibration anaesthesia	Vibration anaesthesia did not reduce pain in venepuncture
(Finken and Mul 2010)	2010	Case report	NA	6 year old	Patient presenting after steroid treatment for keloid	Cushing's syndrome was a complication of the treatment
(Liu and Zhang 2021)	2021	Systematic review	NA	NA	Triamcinolone acetonide and botulinum toxin Type A	A combination of corticosteroid injections and botulinum toxin type A more effective than corticosteroids alone
(Shaarawy et al. 2015)	2015	Randomised double-blind	24	29 years (10-53 yrs)	Intralesional steroid or botulinum toxin type A	Both treatments had a significant decrease in height of lesions and redness
(Khan et al. 2020)	2020	Case series	94	14 years	Excision with steroid injection, compression and radiation therapy as adjuvant therapy	No significant difference between the rate of re-occurrence with different adjuvant therapies
(Wang et al. 2017)	2017	Randomised controlled trial	30	Unknown	Cryotherapy for steroid injection	Cryotherapy reduced pain associated with steroid injections

Table 1. The full list of all articles used in the systematic review.

4. DISCUSSION

Association of Androgen Receptors and Keloids

Asian and African populations are particularly sensitive to the occurrence of keloids (11). Some of the risk factors for keloids include skin tension and infection, genetic predisposition as well as hormonal abnormalities. A study (1) reported an improvement in one their patient's chest keloids after taking Finasteride. Finasteride is a 5-alpha reductase inhibitor that is commonly used to treat Benign prostatic hyperplasia that decreases the conversion of testosterone to dihydrotestosterone (androgen). The study suggests that 'androgen-driven sebum excess may initiate cutaneous inflammation' through a T-cell mediated 'delayed type hypersensitivity reaction' which then subsequently predisposes to keloid production (12). Therefore, the study suggests that decreasing the levels of androgen in the body could be used for the management of keloids. The use of Combined Oral Contraceptives (COCs) could be used in females as an anti-androgenic treatment. However, more research is required to understand sensitivity if keloids to anti-androgenic treatment and identify factors that make keloids more favourable to such treatment.

Management of keloids

There are both surgical and non-surgical treatments available to treat keloids in children as outlined in *Figure 2*. In the surgical excision of keloids, smaller keloids are resected whereas larger keloids undergo a partial or core excision (7). An adjuvant therapy of TCA of 5-20mg dose and CO2 ablation after surgical excision results in 83% of complete clearance of keloids. However, one of the main concerns of the therapy is low adherence as around 33 % of patients were lost in the follow-up period of two years for any further treatment (3). The main side effects of this therapy include hypopigmentation, skin atrophy and telangiectasia (13).

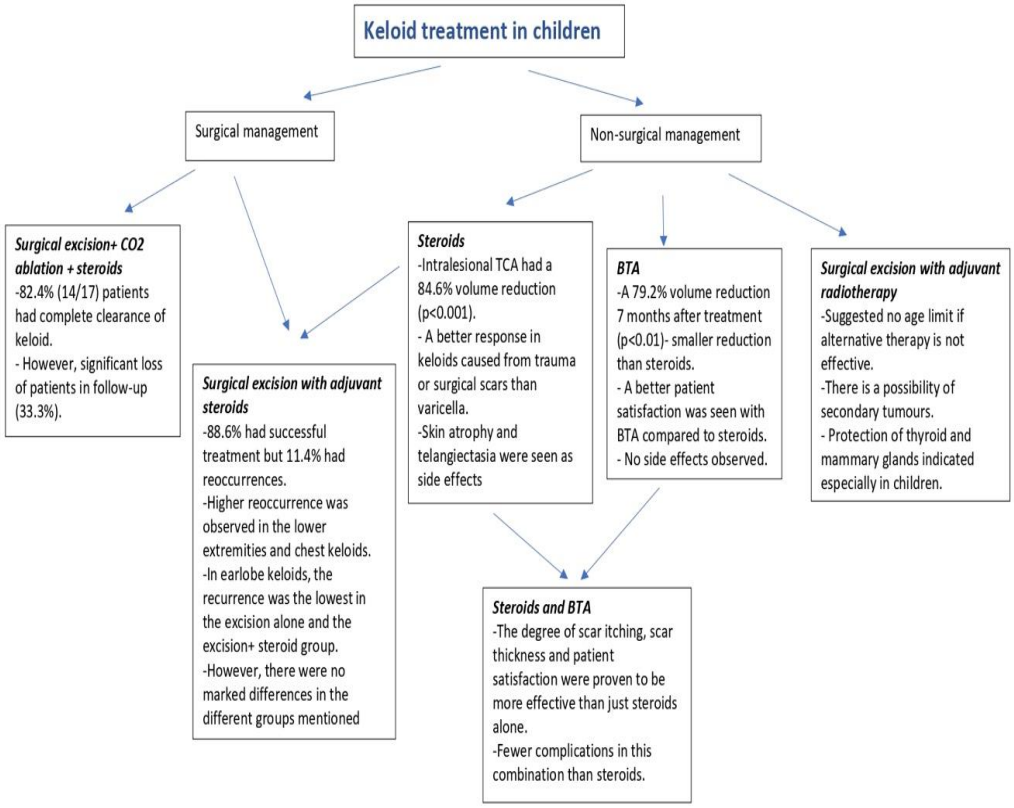

Figure 2. Surgical and non-surgical treatment of keloids in children

Surgical excision

A higher recurrence of keloids was noted in the lower extremity and chest areas despite a combination of surgical excision, full-thickness skin grafting (FTSG), steroid injections or pressure therapy used. An early surgical intervention is not recommended to treat keloids especially in the chest area as they may resolve spontaneously in the paediatric population. Similarly, keloid surgery is recommended in the end of second decades potentially allowing time for the scar to mature enough (6).

Despite penile and genital keloids being uncommon, a case study identified six cases of keloids in the genital area after having surgery for procedures such as circumcision and phalloplasty in gender affirming surgeries or in patients with Androgen Insensitivity Syndrome patients. They were able to successfully treat all of these keloids using excisional, intralesional steroid injections, grafts or silicone gel (2).

Intralesional triamcinolone acetonide (TCA)

The use of intralesional triamcinolone acetonide (4-40 mg range) reduces the volume of keloids 83%. The reoccurrence rate after a TCA treatment was only 4%. Follow-up injections are recommended where the number of injections may vary from 1-5 injections in total. There is no evidence of a greater volume reduction in keloids if the treatment is started early (14).

Botulinum Type A (BTA)

Both TCA and BTA significantly reduces the volume of keloids. It was also noted that there was significant softening, reduction in height and redness of the keloids after treatment with TCA and BTA. The side effects observed in BTA is low/absent when compared to TCA however, this treatment is more expensive than using steroids (13). Despite steroids being proven to be an effective treatment for keloids by many studies, a combination of steroids and Botox appears to provide more significant improvement in the above-mentioned parameters as well as patient satisfaction when compared to corticosteroid use alone. However, the long-term effects of botulinum toxin Type A still needs to be researched through longer follow-up times (8).

Radiotherapy

Radiotherapy under an optimal dose (30 Gy-maximally effective dose) is also recommended as an adjuvant therapy if the alternative therapies are not effective. The optimal dose can be adjusted to the site of the keloid according to their reoccurrence susceptibility. It is a recommendation to provide adequate protection to the thyroid and mammary glands especially in children since there is a low risk of secondary carcinogenesis (7, 15).

Newer therapies- laser therapy

A study (16) that looked at the use of laser therapy (including 585-nm PDL) plus 5Flurouracil (5-FU) concluded that it was unclear if this treatment had a better improvement hypertrophic and keloid scar compared to TAC plus-FU as the ‘certainty of evidence assessed was very low’. Some of the adverse effects mentioned from laser therapy include pain, atrophy, telangiectasia including hyperpigmentation and depigmentation. It can be concluded that there is insufficient evidence for the effectiveness of laser therapy to treat hypertrophic and keloid scars in the study.

Therefore, further high-quality trials are required.

Anti- androgenic treatment

There has been an identified link between excess androgen that increases the risk of keloid formation. In a literature review, one patient reported Finasteride helped to ‘relieve the texture and pruritus of his chest keloids’ (1). The review also concludes that patients who have multiple keloids (2 or more keloids) with typically excess androgen (in conditions such as androgen insensitivity syndrome) ‘may respond well to anti-androgen treatment for their keloids.

Peri-interventional pain management

A topical anaesthetic may be used to reduce the needle-stick pain for intralesional TCA injections especially in the sternum and auricular keloids. However, it has not demonstrated to reduce pain during the procedure (17) therefore, pre-treatment with cryoanaesthesia may be more efficient to manage pain during keloid treatment (10). Vibration therapy for pain management in children has not been shown to be effective (18, 19).

A prospective study (17) looked at the efficacy between the use of local anaesthetics (LA) injection vs the use of topical lidocaine (EMLA) in the pain management of TAC injections for keloids. The study stated that the LA injection was reported to have a significant pain relief ($p<0.001$) in patient than the EMLA. The LA also had an advantage of time efficiency as the EMLA was required to be used at least 1 hour before the TAC injection. However, study (17) found no significance between the use of 1% lidocaine and EMLA in decreasing both the needle-stick pain and pain during injection. Cryoanaesthesia could also be a proposed pain relief option as Wang et al found that there was a reduction in Visual Analogue Score (VAS) pain scores reported by patients compared to non-pretreated areas ($p<0.01$).

A Plastic Surgery Department in London also offer to have intralesional steroid injections for keloids as a day case admission

under general anaesthetic if they are 'younger children unable to tolerate the injections in clinic'.

5. CONCLUSION

There are several surgical and non-surgical treatments demonstrated to treat keloids in children. Surgical excision seems to be the primary therapy for keloids however, this review has highlighted that a "wait and see" approach should be taken when considering surgery for keloids in children. Corticosteroid injections are one of the most common adjuvant therapies being used due to their high effectiveness however, it may not be popular due to its side effects and pain in the paediatric population. Botulinum Toxin Type A has shown to offer the same effectiveness as corticosteroid injections for keloid treatments in preliminary studies however, the long-term benefits are yet to be studied. Several studies have suggested an increased risk of keloid formation with increased androgen (male sex hormones). Treatments aiming to decrease the level of androgens (using Finasteride in males or Combines Oral Contraceptives

(COCs) in females) could provide 'long term benefits to those predisposed to the development of keloids' (1). Patients with Androgen Insensitivity Syndrome (AIS) who choose to undergo gender affirming surgeries may have an increased risk of genital keloids. Therefore, the use of anti-androgenic treatment such as Finasteride or COCs may be used along with surgical/ corticosteroid injections for their keloids.

Pain management is difficult during keloid treatments however, cryoanaesthesia has shown to reduce pain during intralesional triamcinolone acetonide in adults. Therefore, these strategies should be researched for the paediatric population during keloid treatment. The use of LA injections is also proven to be effective in peri-interventional pain relief. Therefore, we would like to see if this can be an effective intervention for pain relief in the paediatric population in a larger scale perioperatively.

6. DECLARATIONS

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Conflicts of interest: None declared

Ethical approval: Not required

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