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Is the Use of Triamcinolone (TAC) in Combination with 5-Fluorouracil (5-FU) More Effective than TAC Alone in the Treatment of Keloid Scars?

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Is the use of triamcinolone (TAC) in combination with 5-fluorouracil (5-FU) more effective than TAC alone in the treatment of keloid scars?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of the selective EBM review is to determine whether or not "Is the use of triamcinolone (TAC) in combination with 5-fluorouracil (5-FU) is more effective than TAC alone in the treatment of keloid scars?"

Study Design: Review of two (2) published, randomized control trials (RCT) and one (1) published, observational case control study (OCCS) in 2009 and 2014. All are in English.

Data Sources: The two (2) RCTs and the OCCS. Both were found using PubMed.

Outcomes Measured: Reduction in scar height and evolution of symptoms, specifically pain and pruritus. Other outcomes measured were erythema, length, width, height, and patient assessment.

Results: In the RCT by Khan at al., (2014) a larger reduction in scar height was found in the group that used the combination TAC + 5-FU, in comparison to TAC alone. In the OCCS by Darougheh et al. (2009) there was more significant improvement in height, width, length, and erythema in the group that used TAC in combination with 5-FU. Good results were concluded for self visual assessment showing greater satisfaction with the TAC + 5-FU group. In the RCT by Davison et al. (2009), the participants who had the greatest improvement in scar height of 92% underwent the treatment 5-FU with excision (group 1). The second group, which involved the use of 5-FU without excision, showed only 81% improvement. The third group, which involved TAC with excision, showed 73% improvement.

Conclusions: Both randomized control studies and clinical control study indicate that 5-FU + TAC is a more successful in regards to scar height and erythema in comparison to TAC alone.

Keywords: keloid, triamcinolone, 5-fluorouracil

Introduction

Keloid scars are a dermal fibro-proliferative lesion that grows outside the margins of the original injury due to an abnormal wound healing mechanism.[1] To susceptible individuals the boundary of the original break in the skin results in an excess of collagen deposition. [2] This type of scar formation is hereditary and has proven to affect men and woman equally.[1] Keloids have been shown to be present in 5-15% of wounds, making the focus on treatment even more pertinent. [2] These lesions have a higher propensity for persons with darker pigmented skin, especially persons of African American and Asian decent. [3] While there is no definitive treatment for keloid scars, multidisciplinary treatment has been investigated. This paper evaluates two randomized control trials (RCTs) and one observational case control study comparing the efficacy of triamcinolone (TAC) alone or in combination with 5- fluorouracil (5-FU) in the treatment of keloid scars.

Keloids occur on the site of local skin trauma, such as a laceration, ear piercing, burn, or inflammatory skin conditions such as acne. This alteration in wound healing is more often seen in people aged 10-30 and rarely presents in the children or the elderly. [2,3] Keloids are also prominent during puberty and pregnancy, which suggests a hormonal component is at play as well as melanin/melanocytes in the wound healing process. [1,3] While keloids do not have malignant potential they often can be disfiguring and a cosmetic distress for many people. They are often asymptomatic, but have potential to be painful and pruritic. [1] These lesions also have the potential to cause functional impairment, depending on their location on the body.

While keloid scars are not a medical emergency or a concern for most people, they are still certainly important in particular fields of medicine such as dermatology or plastic surgery. No studies have been published discussing the number of healthcare visits caused by keloids.

Because of the hereditary nature of keloids, they can place a high financial burden on families where multiple generations are affected. Conventional treatments for keloids including intralesional steroid injections can easily cost hundreds of dollars based on the size and location of the scar.[4] For example, the mean cost for treatment of keloids on the back of the head in one study was found to be $776.93.[4] Multiple sessions over a long period of time are usually also necessary, and negotiating treatment coverage with insurance companies can potentially be challenging for some individuals.

The exact mechanism of keloid scars is not completely understood, but it is known to alter the wound healing process. Unlike the normal wound healing cycle of proliferation, stabilization, and involution, keloid scars undergo proliferation for a longer period of time before stabilization. [5] There is an overexpression of fibroblasts and collagen synthesis, with alterations in growth factors. This all contributes to irregular scar formation, abnormal bundles of collagen, and thickened fibrous tissue. The cells of a keloid scar are observed to have a decreased propensity to undergo apoptosis. They tend to arise in puberty and pregnancy, which suggest both a hormonal component and that melanocytes/melanin play a significant role. [2] The appearance of keloids varies but they often appear as raised, hyper pigmented and waxy, with smooth nodules commonly found on areas of increased tension, such as the sternum or shoulder. Keloids are also common on the face, neck, and earlobes, especially those with piercings. [1,6]

The treatment of keloid scars is still in the trial stage. Some first line, non-invasive treatments include occlusive silicone dressing and mechanical compression therapy. Intralesional corticosteroids (triamcinolone) and laser therapy are other popular alternatives. Refractory keloids and emerging treatments include excisional surgery, radiation, and antineoplastic, such as 5-flurouriacil and bleomycin, which are utilized in treatment algorithms. [2,5]

The aforementioned treatment options have not proven to be definitively effective. Thus, there is no definite first line approach. However, many of the different medications and treatment modalities have been studied alone and in combination with one another to find the best approach to management these scars. The use of TAC in combination with 5-FU has been shown to be effective in the treatment of keloid scars.

Objective

The objective of the selective EBM review is to determine whether or not "Is the use of triamcinolone (TAC) in combination with 5-fluorouracil (5-FU) is more effective than TAC alone, in the treatment of keloid scars?"

Methods

This investigation looks at two randomized control studies and one case control study comparing various outcomes of treatment with TAC alone and in combination with 5-FU. In order to participate in the studies by Khan et al. (Khan) and Darougheh et al.(Darougheh), the patients must not have had treatment on the scars in the last 6 months, or be planning a pregnancy, pregnant, or lactating. Also, Darougheh excluded patients with abnormal liver function or complete blood counts. No exclusion criterion was noted for the study conducted by Davis et al. (Davis). Each study's patients varied in age and ethnicity and compared the use of TAC alone and in combination with 5-FU. In the study by Khan the control group A received TAC only and group B received TAC + 5-FU. In the study by Davison et al. (Davison) each group was given either TAC alone or with 5-FU. Group 1 and 2 both received TAC +5-FU, but differed in excision of the lesion. In the study by Darougheh group 2's results were compared

with group 1, in order to compare the overall difference when 5-FU was used in combination with TAC. The outcomes discussed in this paper were to assess overall reduction in height and evolution of symptoms, specially pain and pruritus.

The author performed searches using PubMed and used the keywords “keloid”, “triamcinolone”, and “5-flurouracil”. The searches were selective to studies in English, in peer-reviewed journals from 2009 to 2014. Inclusion criteria for this paper comprised randomized control trials and case control studies published after 2001. Exclusion criteria included a study with a previous Cochrane review or a student review. All selected articles were based on their relevance to the clinical question and the overall patient oriented outcome. The summary of statistics reported or used in Khan and Darougheh included p-value <0.05, NNT, RBI, and ABI. The demographics of the study are defined below in **Table 1**.

Table 1: Demographics and characteristics of included studies [2,3,6]

Study	Type	# of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Khan MA, (2014)	RCT	150	>12 yo	Patients must have had a keloid 1cm to 5cm in size.	Treatment in the last 6 months, pregnant, lactating, or planning pregnancy.	0	-Group A received intralesional TAC -Group B received intralesional TAC as well as 5-FU. -Both intralesional injections were administered once weekly for 8 weeks.
Davison SP, (2009)	Observational study- CCT	94	All ages	Patients who received either a mix of 5-FU and triamcinolone or steroids alone from 1999-2006	Patients who received TAC and 5-FU without excision. Patients who received TAC injections alone.	0	Patient’s charts were reviewed from 1999 to 2006 of patients who received a combination of 5-fluorouracil (5-FU) and triamcinolone or triamcinolone alone. Follow up period ranged from 6 months to 6 years. Patients were stratified into 3 groups: group 1- combination of TAC + 5-FU without excision, group 2- combo of TAC and 5-FU with excision, and group 3- TAC with excision.

Darougheh A, (2009)	RCT	47	5-70 yo	The keloid has to be a minimum of 10mm in length.	Treatment in the last 6 months, had abnormalities in LFT's or CBC, pregnant, planning pregnancy, or lactating were excluded.	7	Patients were randomly divided into group 1 or 2 and treated weekly for 8 weeks. Patients in group 1 received intralesional TAC and group 2 received the combination of intralesional TAC and 5- FU.

Outcomes Measured

The Khan study measured the reduction in scar height. Photographs were taken before and after treatment for comparison. Assessment of the scar was done at week 4, week 8, and week 12, post treatment. The scar was assessed on a provider graded "five-point observer scar assessment scale" ranging from 0-4 in regards to scar height. The scale was graded as follows: 0- no improvement (no reduction in height of the scar), 1- poor (0-25% reduction in height), 2- fair (25-50% reduction in height), 3- good (50-75% reduction in height), 4- excellent (75-100% reduction in height).

In the Darougheh study, the outcomes addressed were length, height, width, erythema, induration, and pruritus. The scars were also measured by patient and observer assessment of the aforementioned criteria. Assessments of the scars were taken at baseline, week 4, week 8, and week 12 of the study. Length, width, and height were measured using a dial caliper. Erythema was graded by the observer and by the patient, on a 5-point scale in regards to reduction in pigment lightening. A 5- point scale was used as a method of measuring the pigment improvement: 0= no erythema, 1=mild erythema, 2= moderate erythema, 3= severe erythema, 4= very severe erythema. The patient and observer assessment recorded their findings at week 4, 8

and 12 on a 5-point scale defined as no/poor= up to 25% improvement, fair= 26-50% improvement, good= 51-75% improvement, and excellent= 76-100% improvement.

In the Davison study, the outcomes addressed include percentage change in size of keloid and evolution of symptoms specifically, pain and pruritus. Pain and pruritus were reported via patient assessment. Specific tool used in determination of keloid size is unknown. Results were calculated by an independent bio-statistician, who applies an analysis of variance (ANOVA) and an X^2 analysis with s- plus software.

Results

The randomized control study by Khan contained a total of 150 patients (65 males and 85 females) above 12 years old with either a hypertrophic or keloid scar ranging from 1cm to 5cm in size. Group A received intra-lesional triamcinolone (TAC) and group B received intra-lesional triamcinolone as well as 5- fluorouracil (5-FU). Both intra-lesional injections were administered once weekly for 8 weeks. The control group receiving TAC only was compared to the experimental group, due to the experimental groups reduction in scar height. With regards to general effectiveness and overall complications group B proved to show more improvement and have less complications than group A. Frequency of complications in group A were measured at 24% where group B showed only 8%. General effectiveness of the treatment was 51% for group A and 84% for group B. The primary measurement of scar height was measured at baseline, week 4, week 8, and week 12. The average scar height from baseline to the height at week 12 showed a larger reduction in group B. A summary of results can be seen in **Table 2.**

Table 2: Reduction in scar height [8]

	Group A	Group B
Original height	2.387cm	2.713cm
Height at 12 weeks	1.196cm	1.053cm

This study demonstrates that after 12 weeks of intervention with TAC + 5-FU group B experienced greater reduction in scar height than group A which was treated with TAC alone. An ANOVA analysis provided a p value of <0.001 making this finding statistically significant. The numbers needed to treat (NNT) value was 7 so this outcome means that for every 7 participants who received 5-FU + TAC, there was a reduction in scar height when compared to the group only receiving TAC. The control event rate (CER) was 68%, the experimental event rate (EER) was 84%, the absolute benefit increase (ABI) was 16%, and relative benefit increase (RBI) was 24%.

The study by Darougheh had a total of 47 patients enrolled (62.5% female, age range 5-70 years old). Of the 47 that begun the study only 40 completed the treatment along with the 12 week follow up period. Patients were required to have a lesion of 10mm in length or larger. Qualities such as keloid length, height, width, erythema, and visual assessments done by the patients were measured and reported. Length, height, and width were combined into a single category. Group 1 began at 3.7mm in height and displayed a decrease to 2.6mm where group 2 began at 3.3mm and decreased to 1.2mm. Group 2, the experimental group treated with 5-FU and TAC, showed a greater decrease in the entire categories over group 1 (control) at weeks 4, 8, and 12, p value less than 0.05 was reported for all. With respect to erythema, group 1 began at a 3 and managed to rapidly decrease to 1.9 by week 12. Conversely, group 2 displayed a more

gradual decrease from 3.3 to 1.7. Group 1 and 2 both showed a decrease in erythema and showed greater lightening in the TAC + 5-FU group as measured by visual assessment, p value less than 0.01. Both groups displayed a markedly similar reduction in pruritus (p value less than 0.01), unworthy of comparison. The last area of comparison in this study was based on the patient and the observer opinion which showed a greater satisfaction with the combination of TAC + 5-FU, which revealed a patient assessment p value of 0.02. The most common adverse side affected noted in this study was the appearance of telangiectasia's and atrophy, in 37% of the participants. All patients admitted to having pain during treatment, but did not show signs of pigment alteration, ulcers, or erosions. A summary of results can be seen below in **Table 3**.

Table 3 – Changes from baseline to week 12 of treatment.

	Group 1	**Group 2**	**P-value**
Scar size	**3.7mm to 2.6mm**	**3.3mm to 1.2mm**	**<0.05**
Erythema	**Level 3 to 1.9**	**Level 3.3 to 1.7**	**<0.01**
Patient visual self assessment	**20% good improvement**	**55% good improvement**	**0.02**

The p-values for height, width, length, erythema, and patient visual self-assessment were all <0.05 making the findings statistically significant. For this study the most important category that was evaluated was patient visual self-assessment. For the patient self-assessment the control event rate was 0.55 and the experimental event rate was 0.20. The absolute benefit increase (ABI) was 0.35 and relative benefit increase (RBI) was 175%. The number needed to treat

(NNT) was found to be 3 meaning that, for every 3 patients who received TAC in combination with 5-FU, one patient saw visual self improvement described as “good”.

The study by Davison included a total of 94 patients of all ages with 102 keloid scars. Patient’s charts were reviewed from 1999 to 2006 and included patients who received a combination of 5- fluorouracil (5-FU) and triamcinolone or triamcinolone alone, performed by the senior study author. The follow up period for the patients post treatment ranged from 6 months to 6 years. Patients were stratified into 3 groups: Group 1 - (24 keloids) Combination of 5-flurouracil (5-FU) and triamcinolone without excision. Non-surgical patients were treated with intra-lesional injections at 4-week intervals. Group 2 – (52 keloids) Combination of 5-flurouracil and triamcinolone with excision. This group of patients was not randomized because of their inability to undergo surgical excision as per the senior author. These patients received injections intra-operatively and again at week 2, 4, and 6,post-operatively. Group 3 – (26 keloids) Triamcinolone injection with excision. This group was not part of the randomized study because they are considered a non-surgical candidate by the senior study author. This group was small in number and therefore was excluded from the study. Each patient received a different antineoplastic dosage ranging from numerous injections weekly or once per month specifically tailored to the keloid. Triamcinolone injections were kept steady amongst the groups unless adverse drug reactions were noted, in which the steroid dosage was decreased from 40mg/mL to 10mg/mL. The purpose of the study was to compare the results amongst 5-FU and triamcinolone combination in comparison with triamcinolone alone as a treatment modality. Comparisons were also made between group 1 and 2, who both received the combination injection, but differed in excision of the lesion. Of the 3 groups the one that showed the most improvement (92%) in reduction of size was the combination of 5-FU/TAC + excision. Both groups that did not

undergo excision of the scar showed mildly lower improvement in height. Pain and pruritus were measured primarily in the group receiving 5-FU, as there were not enough patients in the TAC only group who had significant enough symptoms to compare. Of the 76 patients treated with 5-FU in group 1 and 2, 93% had resolution of pain and 2 patients either admitted to no change or an increase in pain and pruritus. The most common adverse side affected noted in this study was the development of telangiectasia's in both groups, secondary to the use of TAC. A summary of results can be seen below in **Table 4**.

Table 4: Scar height reduction with regard to time

	6 months- 2yrs	2-4yrs	4-6yrs	Overall
Group 1- % scar reduction with 5-FU/TAC without excision	84%	82%	78%	81%
Group- 2% scar reduction with 5-FU/TAC with excision	95%	94%	90%	92%
Group 3- % scar reduction with TAC with excision	78%	74%	67%	73%

Discussion

The search for an effective treatment for keloid scars is still underway, as no one method has been deemed completely successful to date. The uncertainty of the exact mechanism of how keloid scars form remains incompletely understood, which leads to a questionable line of treatment recommendations.[2] According to Khan, the mainstay of treatment has been TAC, which is associated with numerous side effects such as telangiectasias, pigment changes, and atrophy of the skin.[6] As per Davidson, the use of the antineoplastic/antimetabolic agent, 5-Fluorouracil, has shown to cause the inhibition of collagen synthesis, which is appropriate due to

the excessive fibro proliferative nature of keloid scars. In addition TAC is used in combination with 5-FU, not for therapeutic effects, but rather to reduce local side effects such as erythema and ulceration at the injection site. As the treatment for keloid scars are still being solidified patients are still faced with insurance coverage for treatment. Many insurance companies view these scars as purely cosmetic due to their benign nature and do not cover even the most basic form of treatment such as steroid injections. The ability for patients to receive more extensive treatment with coverage is minimal.

Conclusion

After careful review of the three aforementioned studies included in this meta analysis, triamcinolone (TAC) in combination with 5-fluorouracil shows greater effectiveness in the treatment of keloid scars than triamcinolone alone. In the two RCT studies, the p values that were reported for improvement of keloid scar characteristics and self reported visual improvement were statistically significant. The third study included, a case control study, showed notable improvement of scar height overtime when triamcinolone and 5-FU was compared with TAC alone. The two RCT's had participants from an appropriate and recommended time frame of treatment, 8 weeks, but yearly follows ups would of provided stronger evidence of the long term effectiveness of these treatment options. Limitations for the studies include: relatively small sample size, inconsistencies with gender, race, method of original injury, and location and age of keloid scars. A future study should evaluate whether different injection formulations/dosages and the specific number of treatments needed to achieve improvement for scars of different ages. In addition, more studies addressing pain and pruritus are necessary in order to allow patients who experience discomfort from these scars to have a

medical reason for treatment. Such studies may provide a widely accepted standard of care for treatment of keloid scars.

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