Original Article

Comparison of Efficacy between Triamcinolone and Mixture of Lidocaine-triamcinolone on Keloid Volume Reduction: A Randomized, Double Blinded, Prospective Study

Taweepraditpol S, MD[1], Udkhamtiang W, MD[1]

[1] Plastic and Reconstructive Surgery Unit, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Triamcinolone acetonide intralesional injections have been well established in keloid treatment. Lidocaine has usually been mixed with triamcinolone to reduce pain during the injection. Previous in vitro studies showed that lidocaine could inhibit the fibroblast proliferation. The authors would like to study the efficacy of lidocaine-triamcinolone mixture on keloid volume reduction.

Materials and Methods: Between October 2017 and February 2018, a total 15 patients were enrolled in this study and randomly divided into 3 groups: Triamcinolone (group A), Lidocaine mixed triamcinolone (group B), and Lidocaine with adrenaline mixed triamcinolone (group C). All patients received the treatment a total of 4 times, once every 4 weeks. Then 4 weeks after the last treatment, patients were evaluated for volume reduction using the Vancouver scar scale and Visual analogue score.

Results: No significant volume reduction was observed among the 3 groups (group A: 0.34±0.52 ml, group B: 0.41±0.43 ml, and group C: 0.53±0.93 ml, *p*-value = 0.65). The percentage of volume reduction in group B was noticeable (group A; 47.95%, group B; 62.1%, and group C; 42.07%, *p*-value = 0.521). All patients in group B showed improvement in scar pliability.

Conclusion: Lidocaine-triamcinolone mixture may have higher efficacy than triamcinolone alone in term of keloid volume reduction and scar pliability.

Keywords: Intralesional steroid injection, Lidocaine, Keloid treatment

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Intralesional steroid injection is a standard treatment for Keloids.It works by reducing collagen synthesis, altering glucosaminoglycan synthesis, and reducing production of inflammatory mediators and fibroblast proliferation. The most effective steroid mixture is still questionable in current practice[1,2]. Some physicians prefer using pure steroid injection but others prefer mixing it with lidocaine to lessen pain[1,3]. Previous experimental studies[4,5] found lidocaine could inhibit fibroblast proliferation but there is no clinical study about lidocainetriamcinolone mixture effect to keloid volume reduction.The aim of this study is to the efficacy of lidocaine-triamcinolone mixture on keloid volume reduction.

Materials and Methods

The study protocol for this randomized controlled trial conformed to the 1975 Declaration of Helsinki. It was approved by the Institute Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University. The data collection was performed on October 2017 to February 2018, in a single center, Siriraj Hospital. Informed consent was obtained from all patients in the study. The present study was approved by the Siriraj Institutational Review Board (351/2560(EC4)).

Correspondence to:

Taweepraditpol S.

Plastic and Reconstructive Surgery Unit, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wang Luang Road, Bangkok 10700, Thailand.

Phone: +66-2-4198002

E-mail: ntdclub13@yahoo.com

Patient selection

The inclusion criteria were patients who have been diagnosed with keloid/s, aged >18 years, have not had any treatment for keloids within the last 6 months and no history of drug allergies, specifically to triamcinolone, lidocaine or adrenaline.

We excluded patients who had active infection around keloid area, poor immune status (e.g. during immunosuppressive drug/chemotherapy treatment, End-Stage Renal Disease (ESRD), cirrhosis, autoimmune diseases), pregnancy or lactation.

Randomization and Treatment protocols

The patients were randomly divided into three groups by the RandList computer system (Table 1).

The patients were scheduled for intralesional steroid injection a total of 4 times, once every 4 weeks. They received the ID cards which didn't contain the name or group of the patients. Each visit, the patients were measured for keloid volume with molding and water replacement method[6] and evaluated scar characteristics with Vancouver scar scale[7].

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Then, we applied topical anesthetic cream (lidocaine + prilocaine) around the keloid and waited for 60 minutes before injection. The end point of injection was the total pallor of the keloid. Finally, the pain was assessed with Visual analogue score[8] (Figure 3). Then 4 weeks after the last treatment, the patients were asked back to evaluate final volume and Vancouver scar scale.

If some patients had complete keloid regression or could not tolerate the side effects of the steroid, we would stop injection immediately and submit the outcome for analysis.

Outcome measurement

Primary outcome was keloid volume reduction which was calculated from volume at first visit minus volume at last visit. The volume reduction was also calculated in percentage.

The volume was measured with molding and water replacement method (Figure 1). The molding material was impressed over the keloid to create a cavity, then the cavity was filled with water using a 1cc insulin syringe. The volume of water represented the volume of keloid. Measurement was performed three times and the average of the volume was calculated for analysis.

Secondary outcomes were scar quality improvement which was evaluated with Vancouver Scar Scale[9] (VSS) (Figure 2). Four characters of scar, vascularity, pigmentation, pliability, and height, were analyzed separately on whether it was better or worse after the treatment.

Statistical analysis

The outcomes were presented as mean and standard deviation. To compare the volume reduction and Vancouver Scar Scale among the three groups, Kruskal-Wallis test and Fisher's exact test were employed respectively. All statistical data analyses were performed using PASW 18.0. The *p*-value <0.05 was considered to be statistically significant.

Results

Demographic data

Of the 15 patients who were enrolled into the study, 12 were female and 3 were male. The average age was 39 (16 to 65) years. The most common location of keloid was knee; other areas were face, ear, chest, shoulder and leg. Mean duration of keloid was 14.6 months. The initial size of keloid started form 0.57±0.50 ml in Group A, 0.62±0.210 ml in Group B and 0.98±1.00 ml in Group C which were not significantly different among groups (Table 2).

Table 1. Mixture of steroid solution in each group

Group A	Triamcinolone (40 mg/ml) diluted with sterile water 1:1
Group B	Triamcinolone (40 mg/ml) mixed with 2% lidocaine 1:1
Group C	Triamcinolone (40 mg/ml) mixed with 2% lidocaine with adrenaline (1:100,000) 1:1

Final triamcinolone concentration in all groups was equal to 20 mg/ml

Volume reduction

Mean initial volume was 0.72 ml in this study (0.57 ml in Group A, 0.62 ml in Group B, and 0.98 ml in Group C). Mean final volume was 0.31 ml in this study (0.22 ml in group A, 0.21 ml in group B, and 0.49 ml in group C). The volume reduction in group A was 0.34±0.52 ml, group B 0.41±0.43 ml, and group C 0.53±0.93 ml). The percentage of volume reduction in group A was 47.95%, group B 62.1%, and group C 42.07% (Table 3).

The Kruskal–Wallis test could not find the statistical significant difference among the three groups in terms of initial volume (*p*-value = 1.00), the final volume (*p*-value = 1.00) and the volume reduction (*p*-value = 0.65), However, the percentage of volume reduction in Group B was noticeable.

Vancouver scar scale (Table 4)

Vascularity

Most of the patients started with purple vascularity and improved after treatment, however Fisher's exact test could not find the statistically significant difference among the three groups (*p*-value = 0.53) (Figure 3).

Pigmentation

Almost all patients had hyperpigmentation and

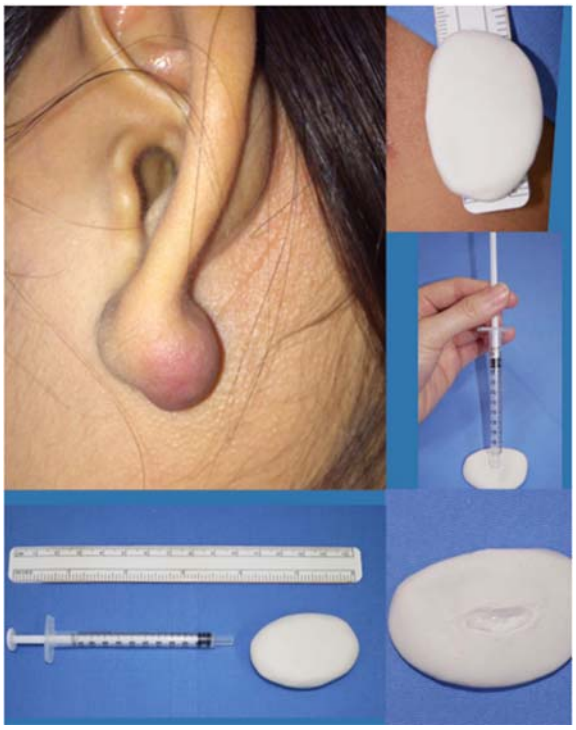

Figure 1. Molding and water replacement method.

had not been better after treatment. There was no statistically significant difference among the three groups (p-value = 0.1) (Figure 4).

Pliability

The majority of patients in this study had yielding and firm pliability, no contracture characteristics. All patients in group B presented better pliability after treatment (100%); however, there was no statistically significant difference among the three groups (p-value = 0.25) (Figure 5).

Figure 2. Demonstration criteria of the Vancouver scar scale[9] (upper diagram) [reproduced from: Sullivan T, Smith J, Kermode J, McIver E, Courtemanche DJ. Rating the Burn Scar. J Burn Care Rehabil 1990; 11(3): 256-60.] and visual analogue score[9] (lower diagram).

Height

Some patients improved in thickness but there was no statistically significant difference among the three groups (p-value = 1.0) (Figure 6).

Pain

Pain scores varied from 0 to 8 among total patients. The scores decreased in later visits. All patients in group B experienced a better degree of pain. There was still no statistically significant difference among three groups (p-value = 0.53) (Figure 7).

Discussion

This is the first clinical study trying to identify the effect of lidocaine on keloid volume reduction. All groups showed reduction in keloid size due to triamcinolone's effect in reducing collagen synthesis, altering glucosaminoglycan synthesis, and reducing production of inflammatory mediators and fibroblast proliferation[7].

The percentage of volume reduction in group B was more than other groups. It might be lidocaine effect corresponding to previous study which showed the lidocaine inhibited fibroblast growth by production of reactive oxygen species (ROS)[4]. However, it might be only just the various response rates of keloid to triamcinolone in the patients that was mentioned as 50 to 100%. In an opposing view, Arnik U, et al[10] mentioned that the lidocaine mixture may be poorer therapeutic outcome than pure triamcinolone due to dilutional effect.

In terms of improvement of the Vascular Scar Scale, the vascularity and pigmentation outcomes were not good whichever mixture was injected. So, we should add other modalities for the patients such as laser therapy[3] or bevacizumab (VEGF inhibitor)[11]. The pliability improvement in Group B was interesting result. Lidocaine without adrenaline made the scar soften. Finally, as to the height, it was hard to say that the height was not improved. VSS was divided the height in range (flat, <2, 2 to 5, and >5

Table 2. Demographic data

	Group A	Group B	Group C	p-value
Sex				
Male	0	2	1	-
Female	5	3	4	-
Age (years)	47 (26 to 65)	32 (18 to 55)	39 (35 to 50)	0.46
Location of keloid				
Face	-	-	1	-
Ear	-	1	-	-
Chest	1	-	2	-
Shoulder	2	1	1	-
Knee	2	2	1	-
Leg	-	1	-	-
Duration of keloid (months)	8.8 (5 to 12)	17.4 (2 to 60)	17.6 (6 to 24)	0.94
Size of keloid (ml)	0.57±0.50	0.62±0.21	0.98±1.00	1.00

Table 3. Initial volume, Final volume and volume reduction

Volume (ml)	Mean ± SD			*p*-value
	Group A (TA)	Group B (TA with Lidocaine)	Group C (TA with Lidocaine with adrenaline)	
Initial volume	0.57±0.50	0.62±0.21	0.98±1.00	1.00
Final volume	0.22±0.23	0.21±0.27	0.49±0.68	1.00
Volume reduction	0.34±0.52	0.41±0.43	0.53±0.93	0.650
Percentage of volume reduction	47.95%	62.1%	42.07%	0.521

Table 4. Vancouver Scar Scale of the patients in this study

Group	Vascularity		Pigmentation		Pliability		Height (mm)	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final
1	Red	Red	Hyper	Hyper	Yielding	Yielding	2 to 5	2 to 5
1	Purple	Purple	Hyper	Hyper	Yielding	Yielding	<2	<2
1	Pink	Pink	Hyper	Hyper	Supple	Supple	2 to 5	2 to 5
1	Purple	Normal	Hyper	Normal	Firm	Yielding	2 to 5	Flat
1	Purple	Pink	Hyper	Hyper	Firm	Supple	2 to 5	<2
2	Red	Purple	Hyper	Hyper	Yielding	Supple	2 to 5	2 to 5
2	Pink	Pink	Hypo	Hypo	Firm	Supple	2 to 5	2 to 5
2	Purple	Purple	Hyper	Hyper	Firm	Yielding	2 to 5	<2
2	Purple	Normal	Hyper	Hyper	Firm	Yielding	<2	Flat
2	Purple	Red	Hyper	Hyper	Banding	Yielding	2 to 5	2 to 5
3	Purple	Purple	Hyper	Hyper	Firm	Yielding	2 to 5	<2
3	Red	Pink	Hyper	Normal	Banding	Supple	2 to 5	<2
3	Pink	Normal	Hyper	Hyper	Yielding	Firm	2 to 5	2 to 5
3	Purple	Red	Hyper	Hyper	Firm	Firm	2 to 5	2 to 5
3	Purple	Red	Hyper	Hyper	Firm	Yielding	2 to 5	2 to 5

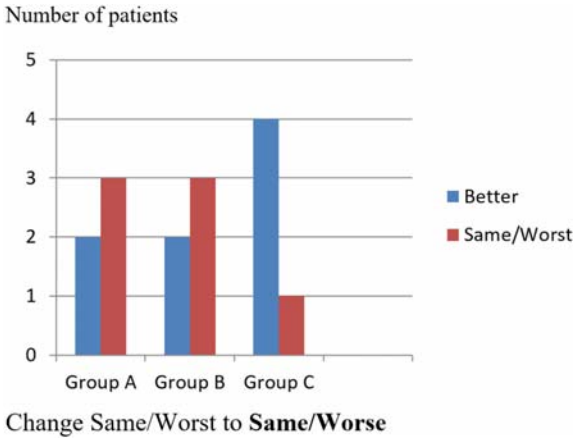

Figure 3. Vascularity between group A, B and C.

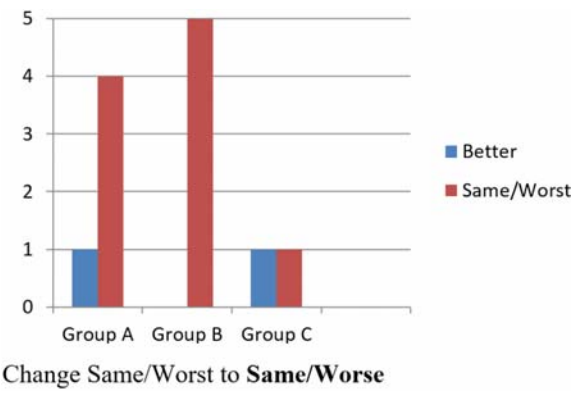

Figure 4. Pigmentation between group A, B and C.

mm) so it could not have detected the better outcome if the scar started at 5 and finished at 2 mm.

About pain, in our protocol, we applied the anesthetic cream over the keloid and surrounding area before injection to lessen pain[10]. However, many patients were still experiencing pain especially on the first visit. Most of patients had less pain in later visits. The pain may be related with the pliability of keloid as if you see that all patients in Group B had softer scars and totally lower pain scores. We thought that hard scars required higher pressure injection and

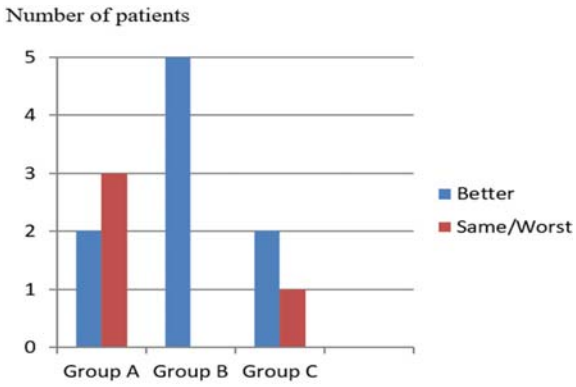

Figure 5. Pliability between group A, B and C.

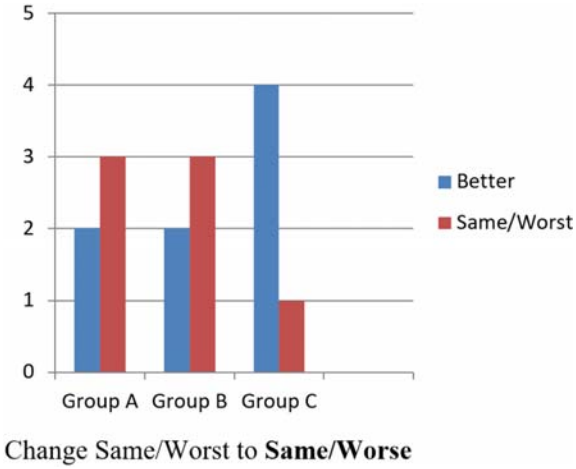

Figure 6. Height between group A, B and C.

this produces the pain.

For the patient's safety, therapeutic concentration of lidocaine varied from 2 to 10 mg/ml. Our study diluted 2% lidocaine in TA (1: 1), so the final lidocaine concentration would be 5 mg/ml which was safe. We controlled steroid concentration equally at 20 mg/ml for all three groups. In current practice, the intralesional steroid injection can be used in 10 to 40 mg/ml. No high level study has proven the most effective concentration[1]. Although some studies showed the lowest recurrent rate when using concentration at 10 and then 40 mg/ml, the methodology was vague[12].

Complications from repeated corticosteroid injections include skin and subcutaneous atrophy, telangiectasia, permanent hypopigmentation, steroid acne, irregular menstruation, and Cushing syndrome. The complications can be reduced by adjusting the dosage and correcting depth to mid-dermis injection[2]. An International panel of experts recommended the usage of corticosteroid doses at 2.5 to 40 mg per site[13].

There are lots of limitations to this study. The

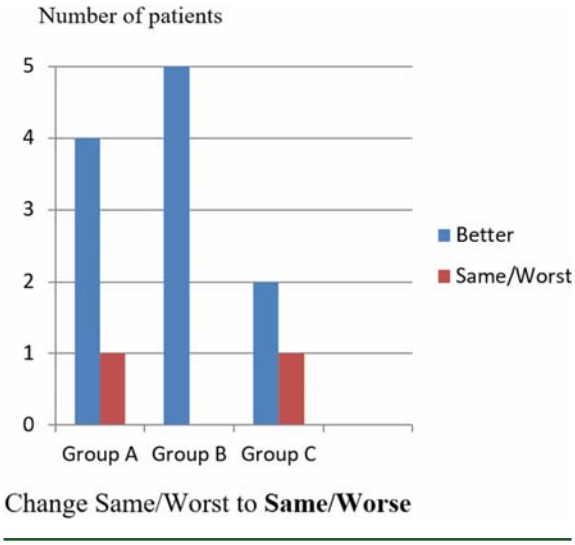

Figure 7. Pain score between group A, B and C.

most important was small sample size. The calculated number of patients was 14 patients per group, but we enrolled only five. If the total number of patients had been larger, the results might have been different. Second, the sites of injection might effect the outcomes but we did not control this issue because of the limited number of subjects. Third, the accuracy of volume measurement was operator-dependent and also flat shape of keloid. Fourth, the Vancouver scar scale was a subjective score also dependent on evaluator. Fifth, multiple factors affected pain score, not only the injected substance. It was also influenced by patient threshold, injection techniques and the location of keloids. Other contributing factors we should be concerned with were the individual response rate to triamcinolone which varied from 50 to 100%, with recurrence rates of 9 to 50% in completely resolved scars[14].

Conclusion

When compared with pure intralesional triamcinolone injection, the mixture of lidocaine-triamcinolone may not be different in keloid volume reduction; however, it may be better in scar pliability. But small sample size, short period of treatment and follow-up time were the limitations of this study.

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What is already known on this topic?

Intralesional triamcinolone injection is one of many

methods for keloid treatment. The purpose of mixing lidocaine with triamcinolone is to reduce pain between injections. There are many in vitro studies showed that lidocaine could inhibit the fibroblast proliferation.

What this study adds?

This study shows mixture of triamcinolone and lidocaine reduce the volume and increase pliability of keloid in vivo study. This mixture may have more benefit than triamcinolone in keloid treatment.

Potential conflict of interest

The authors declare no conflicts of interest.

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การศึกษาเปรียบเทียบประสิทธิภาพระหว่าง triamcinolone กับส่วนผสมของ lidocaine-triamcinolone ต่อการลดปริมาตร keloid

สิทธิโชค ทวีประดิษฐ์ผล, วิลาสินี อุดคำเที่ยง

ภูมิหลัง: การศึกษานี้เป็นการศึกษาเปรียบเทียบประสิทธิภาพระหว่าง triamcinolone กับส่วนผสมของ lidocaine-triamcinolone ในการลดปริมาณ keloid ในผู้ป่วยทั้งหมด 15 คนที่มารับการรักษา keloid ในหน่วยศัลยศาสตร์ตกแต่ง ภาควิชาศัลยศาสตร์ โรงพยาบาลศิริราช ระหว่างเดือนตุลาคม พ.ศ. 2560 ถึง เดือนกุมภาพันธ์ พ.ศ. 2561 โดยแบ่งผู้ป่วยออกเป็น 3 กลุ่ม และได้รับการรักษาโดยการฉีด triamcinolone, lidocaine ผสม triamcinolone และ lidocaine กับ triamcinolone ผสมอะดรีนาลีน

วัสดุและวิธีการ: ผู้ป่วยทุกคนได้รับการรักษาทั้งหมด 4 ครั้ง ทุก 4 สัปดาห์ หลังการรักษาครั้งสุดท้าย 4 สัปดาห์ ผู้ป่วยจะได้รับการประเมินการลดปริมาตรของ keloid, Vancouver scar scale และ visual analogue score

ผลการศึกษา: ไม่พบว่ามีการลดปริมาตรแตกต่างอย่างมีนัยสำคัญระหว่างทั้ง 3 กลุ่ม แต่พบว่าการลดปริมาตรในกลุ่มที่ได้รับ lidocaine ผสม triamcinolone มีมากกว่าสองกลุ่มที่เหลือ นอกจากนี้พบว่าความยืดหยุ่นของ keloid ดีขึ้นในกลุ่มนี้

สรุป: ส่วนผสมของ lidocaine-triamcinolone อาจมีประสิทธิภาพสูงกว่า triamcinolone เพียงอย่างเดียวในแง่ของการลดปริมาณ keloid และความยืดหยุ่นของแผลเป็น