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KELOIDS AND HYPERTROPHIC SCARS;

COMPARISON OF INTRALEISIONAL INJECTION OF TRIAMCINOLONE ALONE AND TRIAMCINOLONE MIXED WITH 5 FLOUROURACIL IN TREATMENT OF KELOIDS AND HYPERTROPHIC SCARS.

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ABSTRACT… Objectives: To compare the effectiveness of triamcinolone alone and triamcinolone mixed with 5-flourouracil used for intralesional injection to treat symptomatic hypertrophic scars and keloids. **Study Design:** Prospective study. **Place & duration of study:** Departments of Plastic and General Surgery, Khawaja Muhammad Safdar Medical College, Sialkot from January 2014 to September 2016. **Material and Methods:** Plastic and general surgery outpatients with symptomatic keloids and hypertrophic scars fulfilling inclusion criteria were registered. Adult patients irrespective of gender, areas involved and size of the keloids were included. Patients refusing treatment, pregnant and lactating women were excluded; similarly the patients not completing the follow up for at least 3 months were dropped from the statistical analysis. Patients' response to treatment was judged by the reduction in the physical size of keloids and subjective improvement in symptoms of itching, discomfort, pain, deformity or redness. Minimum of three sessions of treatment was must for assessment of outcome. Data was entered and analysis done by SPSS v 22. **Results:** Of the 293 outpatients 115 were treated by the mixed triamcinolone and 5 flourouracil while 178 patients were injected with triamcinolone only. Female patients were more in number with ratio of 2.8:1. Good response to treatment with Triamcinolone alone was obtained in 69 (38.76%) while good response was seen in 62 (53.91%) of patients with intralesional Triamcinolone mixed with 5-flourouracil. **Conclusion:** The intra-lesional steroid injection commonly used as its treatment has convincing response. The presently used mixture of steroids and 5-flourouracil has more promising results as regards patients' improvement in symptomatology as well as physical reduction in the size.

Key words: 5-fluorouracil, Triamcinolone, Intraleisional, Keloids, Hypertrophic scar.

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INTRODUCTION

Certain patients have propensity to develop Hypertrophic scars and Keloids. Etiological and inciting factors include local trauma to skin or inflammatory skin conditions after lacerations, tattooing, acne, burns, pricks, and injections, insect bites, piercing of ear lobe, vaccination, abscess or surgical procedure. Abnormal synthesis of dermal collagen fibers is the pathological process for these conditions.[1]

Skin areas of increased tension like Shoulders, sternum, mandible and arms are favorite sites for Keloids. Asians and dark skinned community are more victims. Keloids develop out of the margins of the basic wound and regression with time is not there; so they develop masses like tumors causing disfigurement of the lesion. The collagen arrangement is in completely disorderly with presence of keloidal collagen bundles. Excision of keloids often lands up with its recurrence. Hypertrophic scars keep localized in the vicinity of the surgical wound and there is no change in its shape and fibers are aligned parallel to the longitudinal axis of the wound. Basic etiology of this abnormal healing is not clearly known. Patients seek medical treatment for complaints of itching, pain, restriction of movement and more often for cosmetic disfigurement.[2] Early care of the surgical wound can minimize scarring. Task with small wounds is getting epithelial cover with moist semi-occlusive dressings by the surgeon. Beyond

10-14 days of epithelialization, the formation of hypertrophic scars goes up drastically. Primary closure of an open wound needs attention to the stretch on the wound. Subcuticular stitching using nonabsorbabble suture kept in place for about six months is a good technique. Keeping pressure on the hypertrophic tissue has been reported to be beneficial to avoid recurrence of keloid after surgery. Elastic garments are available for different sites for this prolonged pressure that are prescribed after healing.[3]

Physical therapies using x-rays, electron beams and interstitial radiation have been in practice in the treatment of these problematic lesions. But opinions are different and questions are made over use of these therapies for concerns of harmful effects and risk of malignant potential. Good response in clinical settings can be achieved in doses which are in safe range.[4] Surgical removal done with knife or with use of laser or electrocautery is the other option but the recurrence rate is near 100% for keloids but is better with hypertrophic scars. The results over different areas are promising like ear lobes but it requires proper precautions and strict postoperative treatment. Overall recommendations are to avoid the surgical treatment as far as possible due to its failure. Excision of hypertrophic scars is good in selected cases but requires meticulous surgical technique and allied therapies as radiotherapy, interferon injected in lesions or topical application of steroids.[5]

Intralesional injections of Bleomycin through multiple pricks result in thinning of keloids and hypertrophic scars. Verapamil has a property of inhibiting endothelial growth factor and interleukin-6 has good effect when given intralesionally.[6] Antiproliferative capacity of Interferon α-2b is effective when injected intralesional as one of treatment modality. Freezing using liquid nitrogen can flatten and decrease the thickness of keloids especially on the back in comparison to those of chest wall. Cryotherapy reduces the hardness and it becomes easy to inject other medicines. It is painful and needs local anesthesia. Many studies advocate the CO2 or Erbium YAG laser use the treatment of keloid and hypertrophic scars. Similarly pulsed dye laser (PDL) used in some trials showed encouraging response for softening these lesions.[7] Silicone gel dressings though cumbersome in use but have shown good results in about 50% patients. In all treatment options probably the procedure of continuous pressure and occlusive contact media like silicones is accepted as the one which can manage these scars and at the same time have minimal side-effects.[8]

Intralesional injection of corticosteroid like Triamcinolone Acetate is one treatment which is taken as the most accepted and practiced for keloids. These synthetic medicines can slow or stop the formation of collagen due to its anti-inflammatory effect. Its effect of causing atrophy is the mainstay to get the required result in treating keloids. Multiple doses in the keloid mass at spacing of 4 to 6 weeks is done and effect is achieved. Usually its tough to inject because of hard stony consistency of the keloids.[9] FFU (5-florouracil) resists proliferation of fibroblast in tissue cultures. It is hypothesized that it can lessen post-operative scar formation due to this property. Multiple doses (1-3 weekly) at the start and then these injections are repeated at spaces of 4 to 6 weeks has documented efficiency in cutting down the size of these keloids and hypertrophic scars substantially. The injections of FFU are painful; and pain can be controlled with adding triamcinolone acetonide or separate field block anesthesia is applied. Mixing 0.1 ml of triamcinolone acetonide (10 mg/ml) to 0.9 ml of FFU (50 mg/ml) will reduce pain and also the inflammation. Generally 3 to 10 sessions of these injections are done for complete flattening of these lesions. Patients response as decrease in pain, itching, feel of stretch or pulling, and irritability is first observed then it is proceeded by softening, flattening and decrease in the size of the lesions. Side effects of 5 florouracil injection include pain and stinging, black discoloration, purpuric rash at injection site, and sometimes ulceration.[10]

Keloids and hypertrophic scars are a common entity in our outpatient's department. No study

about this pathology has been carried in our region. This study was planned to see the effectiveness of intraleisional treatment of keloids and postoperative hypertrophic scars, we used two methods of treatment modes and treatment is solely at outpatients department at Allama Iqbal Memorial Teaching Hospital affiliated with Khawaja Muhammad Safdar Medical College, Sialkot. The objective of the current study was to compare the effectiveness of triamcinolone alone and triamcinolone mixed with 5-flourouracil used for intralesional injection to treat symptomatic hypertrophic scars and keloids.

MATERIAL AND METHODS

A written informed consent was taken after relevant explanation to participants about the aims and process of study. No extraordinary facilities or expenditures were directed to patients based on accepting or declining to participate in the trial. In any part of the study, participants could request to leave the study without any limitation or prerequisite. We followed guidelines in the Helsinki declaration.

Irrespective of severity and chronicity of lesions, patients were included using non-probability convenience sampling technique. Study design was prospective. In addition to symptoms and signs, clinical aspects of lesions and the size of scars were recorded using a questionnaire. In patients with more than one keloid and post-operative hypertrophic scars, the most accessible one with a defined size preferred by the patient was considered for the treatment. Pregnancy or lactating patients as well as those with diabetes mellitus, cancers and cardiovascular diseases were excluded. Post acne scars were also excluded. All patients underwent regular visits after therapy every three weeks for evaluation of the treatment progress. The process was performed until the scar became flat unless having no response after six months, leading to treatment discontinuation and considering the patient as non-response case. The participants were followed up for at least 3 months to evaluate disease improvement and adverse effects or recurrence.

In group I, triamcinolone acetonide 40 mg/mL suspension was diluted with lidocaine hydrochloride 2% to achieve a dose of 20 mg/ml. Effect of causing atrophy, one of the actions of steroids, is used to get therapeutic response in keloids or hypertrophic scars. Multiple injections in the scar bulk at intervals of 4 to 6 weeks were made to get the final response.

In groups II; mixture of 0.1 ml of triamcinolone acetonide (10 mg/ml) and 0.9 ml of 5 florouracil (FFU, 50 mg/ml) was used and at multiple sessions with interval of 3-4 weeks to get maximum flattening of these lesions. Subjective improvement was noted for stretching and pulling sensation, pain, discomfort and pruritis firstly and then noting softness and flatness of lesion. Thickness, pliability, vascularity and pigmentation are the four parameters of checking the effectiveness. The Centimeter Scale was used means to report size of scars and keloids.

Both the groups were classed to have response as no response, mild response, moderate and good response as reduction in size by <10%, <25%, <50% and more than 50% respectively. Minimum of three sessions of treatment was must for assessment of outcome. Data was entered on a proforma and analysis of variables done by SPSS v 22.

RESULTS

Table-I shows general demographic data of the patients included in the study. This data compiled after exclusion of the patients not fulfilling our criteria. 293 patients were included in the study. Mean age of the patients was 35.13±11.37 years with range from 18-65 years. There were more females as compared to males. Male to female ratio was 1:2.8. In group I there were 178 (60.75%) patients while in group II there were 115 (39.25%) patients.

Sternum (33.44%) and shoulder (20.13%) were the most common sites. Ear lobe, nape of neck, upper and lower limbs were involved in (9.55%), (8.53%), (6.48%) and (5.46%) of cases respectively. 48(16.38%) were miscellaneous sites Table-II.

Total no of patients in Study	293	100%
Age in years	Range 18-65	Mean 35.13±11.37
Gender	Male : Female	(1: 2.8)
Group I- Triamcinolone alone	178	(60.75%)
Group II- FFU and Triamcinolone	115	(39.25%)

Table-I. General Data

Sternum	98	33.44%
Shoulder	59	20.13%
Ear lobe	28	9.55%
Nape of Neck	25	8.53%
Upper limb	19	6.48%
Lower limb	16	5.46%
Miscellaneous	48	16.38%

Table-II. Sites of keloids and hypertrophic scars N=293 (100%)

Patients presented with either one symptom or more than one symptom. The most common symptoms in both groups were itching (42.13%) Vs (61.73%) redness (47.75%) Vs (54.78%) and pain (31.46%) Vs (40.86%). Discomfort/ burning sensation was (23.59%) Vs (33.91%) and disfigurement/deformity was (16.26%) Vs (18.26%) in each group Table-III.

Symptoms	Group I- Triamcinolone n=178	Group II- Mixed FFU n=115
Itching	75(42.13%)	71(61.73%)
Redness	85(47.75%)	63(54.78%)
Pain	56(31.46%)	47(40.86%)
Discomfort/ burning sensation	42(23.59%)	39(33.91%)
Disfigurement/ deformity	29(16.26%)	21(18.26%)

Table-III. Presentation of the patients N=293

There was very little difference in group I and group II patients in terms of no response and mild response 10.67% Vs 7.82% and 19.66% Vs 20.00%. Group I patients favored the category of moderate response 30.89% Vs 18.26% in group I. The patients who showed good response belonged mostly to group II 53.91% as compared to 38.76% in group I Table-IV.

Effectiveness (reduction in size)	Group I- Triamcinolone - n=178	Group II Mixed-FFU n=115
No response (<10%)	19(10.67%)	9(7.82%)
Mild response (<25%)	35(19.66%)	23(20.00%)
Moderate response (<50%)	55(30.89%)	21(18.26%)
Good response (more than50%)	69(38.76%)	62(53.91%)

Table-IV. Treatment outcome

DISCUSSION

Keloids and hypertrophic scars which were resistant to the treatment and fell in the category of no response were referred for surgical treatment and radiotherapy. We had good response with mixture of triamcinolone and 5 florouracil in 62 (53.91%) patients; comparative results were shown by Xu et. al.[11] but they used intralesional injection of steroids, IFN-α2b and verapamil in keloid and hypertrophic scar. Margaret Shanthi and colleagues[12] studied comparison of intralesional injection of triamcinolone and verapamil in 54 patients with keloid. Improvement in clinical characteristics were improved using both drugs for three weeks; our study has same findings but we encountered few drug reactions while these reactions were reportedly higher in their study.

We did not cater for post surgical injections or combined with surgery trials while many researchers have used these steroids and even verapamil after surgery like the study of D'Andrea et al[13] comparing the effectiveness of intralesional verapamil hydrochloride in two groups after perilesional surgical excision of keloids and found 54% success rate in combined therapy with surgery and verapamil, but 18% in surgery in addition to topical silicone without verapamil. Similarly, Lawrence used intralesional verapamil hydrochloride after earlobe surgical keloid excision revealed a 52% cure rate in 35 African-American patients.[14]

Ahuja et al[15] compared the effect of Triamcinolone and verapamil injections for treatment of keloid concluding that verapamil is the best choice for flattening the raised scars; our results 62 (53.91%)

also speeks of that mixture of Triamcinolone and 5 florouracil is as good as verapamil for hypertrophic scar flattening. Our study shows that intraleisional therapies using mixtures in keloid lesions have superiority over single agent therapy preferably with intralesional injection of regard, triamcinolone and 5 florouracil have lesser reactions and more effective than triamcinolone alone which have slightly slower effect.

CONCLUSION

Keloids is quite a common pathology encountered in general surgical and plastic surgical practice. The patients usually present due to their apprehension and opt for treatment due to varied symptoms. The intralesional steroid injection commonly used as its treatment has convincing response. The presently used mixture of steroids and 5-flourouracil has more promising results as regards patients' improvement in symptomatology as well as physical reduction in the size. This mixed injection may gain popularity in the times to come.

Authors contributions

All authors searched the literature, coordinated the writing and submission of the study. Reading and approval of the final manuscript was done by all authors.

Disclosure of interests

There is no conflict of interests and no funding received from any pharmaceutical companies for the study.

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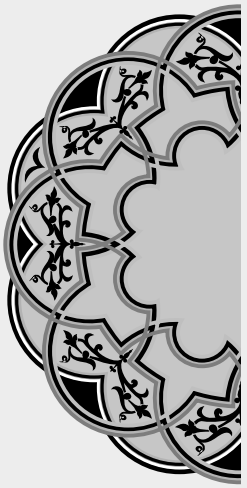

"You always have a place to run to, always. The place is GOD."

Unknown

AUTHORSHIP AND CONTRIBUTION DECLARATION

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