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Original Research Article

Therapeutic evaluation of various modalities in keloid

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ABSTRACT

Background: Keloid is deregulated fibroproliferative growth in response to tissue injury. Keloids are known for their stubborn nature and present as therapeutic challenges in practice. Aim of our study is to evaluate various treatment modalities for search of treatment which stand out with maximum efficacy and least side effect.

Materials and Methods: 120 patients with presternal keloid (female and male, aged 18-60 years) were recruited to receive one of the five treatment methods which were(1) Cryotherapy,(2) Cryotherapy and intralesional Triamcinolone acetonide,(3) Cryotherapy and intralesional 5- Fluorouracil(4) Cryotherapy and combination of Intralesional Triamcinolone acetonide with 5- Fluorouracil(5) Cryotherapy and Intralesional Triamcinolone acetonide combined with Silicone gel sheet application in each group respectively. Evaluation done by the Patient and Observer Scar Assessment Scale (POSAS) score at every 3 week till 6 months.

Results: Patients with significant improvement (> 50% reduction in POSAS) were 42%, 75%, 75%, 85%, and 90% in each 5 group respectively. Side effects like Hypopigmentation and Skin atrophy were significantly much frequent in group 2 while skin ulceration and pain were common with group 3. Group 1 showed maximum recurrence of lesion while no recurrence was seen in group-2 and 5 even after 3 month of post treatment.

Conclusion: Among nonsurgical treatment modalities, Cryotherapy along with intralesional medication like triamcinolone acetonide and 5 fluorouracil and adjuvant therapy like silicone gel sheet are promising, inexpensive and an effective OPD based treatment that provide good alternative for keloid treatment in comparison to surgical procedures.

1. Introduction

Keloid is an overgrowth of fibrous tissue develops after healing of skin injury in the form of trauma, inflammation, surgery, or burns represent abnormal wound response in predisposed individuals, extends beyond the borders of the original injury, doesn't regress spontaneously and tends to reoccur after excision. They cause cosmetic disfigurement and are often associated with pain or pruritus especially when actively growing.[1,2] Keloids, as has been reported,[3] has been shown to be composed of large, thick collagen filaments of both types I and III collagen. In addition, the fibroblasts that are present in keloids tend to persist longer than those of normal skin and have been shown a fourfold increase in fibronectin production and affect the overall healing process of the scar.[4] Numerous remedial agents have been used for the treatment of keloids and hypertrophic scars. One of the interesting facts that have been brought out in numerous clinical studies is that recurrence of keloid, no matter what the treatment, is common with monotherapy. With the use of Combination

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remedy we can increase treatment response rates and achieve a desirable result in dealing with these lesions. Injectable 5-fluorouracil (an antimetabolite that suppresses fibroblast proliferation), triamcinolone acetonide (an anti-inflammatory agent), cryotherapy (an agent that has been shown to dissolve fibrous bands by cryolysis) and silicon gel sheet application (maintain hydration of scar and increase pliability), all of these agents have been tried individually or in combination of two of the agents in earlier clinical trials with somewhat encouraging result.[5] It is found that the use of multimodalities in treatment option was statistically significant in reducing the signs and symptoms of the keloids.

2. Aims and Objectives

To determine the safety and efficacy of various treatment modalities of keloid.

3. Materials and Methods

The study was conducted upon 120 patients who aged between 18-60 years and clinically diagnosed with keloid over presternal region with size 3 to 6 cm in greatest dimension and less than equal to 5 year of duration who had received no treatment in last 6 months came to Outpatient Department of dermatology, venereology & leprosy, in a Tertiary care center during July 2017 to June 2020.

Detailed history and demographic parameters such as patient's age, sex, and duration, number of lesions, family history and treatment history were recorded. Complete physical and systemic examination and basic investigations like complete haemogram, blood sugar, liver function test, renal function test, HIV I and II and HbsAg were carried out at the commencement of therapy. Patients with diabetes mellitus, hypertension, HIV, hepatitis B, bleeding disorders, pregnant or lactating women, and those with unrealistic expectation were excluded from the study. An informed written consent for the study was taken from the patients who were selected for study. The photographs of keloid were taken before treatment was initiated and in subsequent visits during the course of treatment. Complete blood counts were done at 0 and 12 weeks and at the end of the therapy.

All the patients were informed regarding the nature of the disease, course and prognosis. They were also explained regarding the need for consistent and prolonged treatment. Approval for conduction of the study was obtained from the institutional ethical committee. .

Based on sigma six online sample size calculator at 98% CI, margin of error 1%, SD0.7: total sample size made was 120; patients were randomly allocated to one of 5 groups with 24 patients in each group by simple random sampling technique.

In first group patients received cryotherapy with liquid nitrogen by cryogun, two freeze thaw cycles of 15 seconds each were given by cryogun keeping the cryoprobe 2 cm away from the keloid. In second group patients were initially treated with cryotherapy same as given in first group and immediately after 10 minute intalesional injection of Triamcinolone acetonide (TAC) in concentration of 40mg/ml was given, In group 3 patients initially treated with cryotherapy same as previously and immediately followed by intralesional injection of 5- Fluorouracil in concentration of 50mg/ml. Group 4 received cryotherapy and combination of Intralesional Triamcinolone acetonide In concentration of 0.1ml (40mg/ml) and 5- Fluorouracil injection in concentration of 0.9ml (50mg/ml). While in Group 5 after cryotherapy immediately given intralesional injection of Triamcinolone acetonide in the concentration of 20mg/ml and Silicone gel sheets were applied over the lesions and kept in place by micropore, patients were told to ensure that silicone gel sheet was to be kept on the keloid throughout the day and only to be removed while taking bath. Drugs were delivered with a 27 gauge needle attached to an insulin syringe. 0.2ml was injected so as to cause blanching at each site 1cmapart sequentially, and the entire lesion was covered. Care was taken not to cause blanching of the surrounding area. Pressure hemostasis was obtained and antibiotic dressing was done if needed.

Patients in all groups received treatment at 3 week interval for six months or till the keloid resolved and were followed up for further 3 months after last treatment session.

Treatment response was evaluated by the Patient and Observer Scar Assessment Scale (POSAS)[6] which has two scales: the Patient Scar Assessment Scale (PAS-patient scale) and the Observer Scar Assessment Scale (OAS-observer scale). The scar was rated numerically on a ten-step scale (with 10 indicating the worst imaginable scar or sensation) on six parameters: vascularity, pigmentation, thickness, relief, pliability, and surface area on the observer scale. Apart from the color, stiffness, thickness, and irregularity of the scar the Patient Scale consist two additional parameters which were pain and itchiness.

Evaluation was done by two independent observers and the patient who was blinded to the treatment groups and independently gave their overall opinion on the appearance of scar, with score ranging from 1 to 10. The total scores was obtained by adding the scores of each of the 6 items (range, 6-60), with higher the scores indicating the worst imaginable scar.

The treatment response was graded based on improvement in POSAS score as follows: Poor response: Up to 25% improvement; Fair response: 26% to 50% improvement;Good response: 51% to 75% improvement and Excellent response: 76% to 100% improvement while Overall Improvement was assessed with respect to POSAS score of vascularity, pigmentation, thickness, pliability, and symptoms like itching and pain as well as recurrence of lesion. Chi-square test was performed for comparing the

scar improvement and side effects among various groups. A P value <0.05 was considered to be statistically significant. >50% reduction in POSAS score considered as significant improvement in this study. Study was primarily ended when remission of the keloid occurs or after 24 week of treatment whichever was earlier or study withdrawal due to unaccepted side effect was observed.

After completion of therapy, all patients were followed up after 3 months to check for recurrence of lesions.

4. Result

Out of 120 patients, 100 were completed the study; in which 51(51%) were males and 49(49%) were female; mean age group comprise between 21-30 year. A positive family history was observed in 12(12%) patients. Prominent portion of participants reported itching (55%) followed by pain (8%) in keloidal lesion. out of 24 patients recruited in each group 19, 20,20,21,20 patients completed the study in groups 1, 2,3,4,5, respectively. Most of the patients with had Fitzpatrick skin type 3 and 4 and none of the patients in the study showed hematological abnormality during the study.

Out of 100 patients, 43 of keloid was spontaneous in nature while infection (20%), post inflammatory (15) and trauma (10%) were the common factor observed which trigger the keloid formation.

Mean POSAS of all parameters while overall mean POSAS of each treatment groups were shown in Table 2.

Table 1 Showed changes in mean POSAS of individual parameter from base line to end of the study at 24 weeks.

Treatment response in each study groups were shown in Table 4.

Treatment response in the form of significant improvement (>50% reduction in POSAS) was shown in Table 5.

4.1. Group 1

During a period of 24 weeks 21% (4/19 patients) failed to be treated with cryotherapy, although significant decrease in POSAS score was absolutely reported in responsive case (8/19) (P <0.05) as a single modality for treatment cryotherapy show good therapeutic response in small and younger keloid (<2 year of origin) (p<0.05)

4.2. Group 2

0ut of 20 patients, 15 (75 %) patients showed good to excellent response while 2(10%) had no improvement. Reduction in scar thickness and improvement in pliability, vascularity were significantly faster in this group as compare to other groups but adverse effect profile was highest with this group. (P value= <0.05)

4.3. Group 3

Overall 15/20 patients (75%) showed good to excellent response and 3/20 patients (15%) had no response to treatment. POSAS score star to show improvement at 15th week than group 2.

4.4. Group 4

This group received cryotherapy plus combination of triamcinolone and 5 FU as treatment. 18/21 patients (85%) showed good to excellent response and 1 patient (4.7%) had as poor response to treatment. This group show similar treatment response to group 3 but had lesser side effect than group 3 (p<0.05)

4.5. Group 5

All 20 patients in this group who treated with combine treatment modalities of cryotherapy+ triamcinolone acetonide (20mg/ml) + silicone gel sheet show significant improvement(P<0.05), in which 18/20 patients (90%) had good to excellent response. This group also showed over all faster improvement in pliability, vascularity and thickness along with group 4 and 2.

Itching was significantly reduced in all the 5 groups. In this study Irrespective of the group there was overall 75% good to excellent response, 15% Fair response, and 7% patients had Poor response patients with Good to excellent treatment response (>50% improvement in POSAS) were 42%,75%,75%,85%,90% respectively in each group though rate of responsiveness seemed to have no significant difference between the groups except group 1.

All treatment modalities were well tolerated. Immediate side effects observed within 24 hour were erythema, edema and bulla formation in most of all groups which were well managed symptomatically while remote side effects noted were –hypopigmentation, telangiectasia, atrophy and ulceration. Pain in mild to moderate severity and erythema experienced immediate post treatment subsides by itself and relived by taking pain killer medication within hour. None of the patient dropout due to such side effects. Mild Pain at injection side and cryotherapy side was the most frequent complaint in all participants (100%). Group 2 showed significant side effect like depigmentation and telangiectasia and atrophy at injection side in 20/20 (100%) patients (p<0.05); same as pain and ulceration were seen in group 3 which was significantly decrease in group 4 (p<0.05). Other adverse effects are presented in Table 6 showed graphical presentation of side effects.

All the patients were followed up 3 months after the last treatment session which was at 36^{th} week to see the recurrence of lesion in which maximum recurrence was seen in group-1 in 15/19 (78%) of the patients followed by group 3 in 3/20 (15%) patients and least in group-4 which was in 2/21 (9.5%) of patients. No recurrence was seen in group-2

Table 1: Mean POSAS score of parameter in study groups

Parameter	Group 1		Group 2		Group 3		Group 4		Group 5	
	Base line	24 week	Base line	24 week	Base line	24 week	Base line	24 week	Base line	24 week
Vascularity	6.65	3.3	5.8	2.15	5.8	2.5	5.55	2.6	5.7	2.95
Pigmentation	1.65	3.23	1.3	6.5	1	3	1.15	3.05	1.2	3.2
Thickness	6.15	3.45	6.4	1.8	5.95	2.3	6.6	2.1	6.86	2
Pliability	6.65	3.45	6.6	1.75	6.3	2.05	7	2.55	6.8	1.55
Itching	3	1.5	3.1	1.05	2.4	0.95	3	1	2.9	1
Pain	1.1	1	1.1	1	1	2.8	1.55	1	1.15	1
P value	<0.05		<0.05		<0.05		<0.05		<0.05	

Table 2: Mean Patient and Observer Scar Assessment Scale (POSAS) score in study groups

Group	Average Posas								
	Base Line	3 Week	6 Week	9 Week	12 Week	15 Week	18 Week	21 Week	24 Week
1	52.65	47.5	40.1	35.55	33.8	31.85	30.35	28.75	25.15
2	51.8	42.75	36.85	35.5	31.2	28.95	27.45	26.4	25.35
3	50.1	40.15	35.35	29.4	26.85	25.3	24.3	23.1	22.9
4	52.15	38.4	32.65	29.9	26.4	25.3	24.8	22.65	22.75
5	51.03	35.3	30.55	25.7	25.5	24.4	23.55	22.35	21.05

Table 3: Mean OAS and PAS score in study groups

	Group 1		Group 2		Group 3		Group 4		Group 5	
	Base line	24 week	Base line	24 week	Base line	24 week	Base line	24 week	Base line	24 week
OAS	26.5	13.2	25.6	12.95	24.35	11.1	25.75	11.55	24.81	11.35
PAS	26.12	12.95	26.2	12.4	25.75	11.1	26.4	11.2	25.22	10.7

Table 4: Treatment outcomes in study groups

Response	Group										Total	
	1		2		3		4		5			
	No	%	No	%	No	%	No	%	No	%	No	%
Excellent	2	10.52	4	20	3	15	4	20	6	30	19	19
Good	6	31.57	11	55	12	60	12	60	12	60	53	53
Fair	7	36	3	15	2	10	3	15	1	5	16	16
Poor	4	21	2	10	3	15	2	10	1	5	12	12
Total	19	100	20	100	20	100	21	100	20	100	100	100

Table 5: Treatment outcomes in study groups

Group	Patients with Significant Improvement (good - excellent response)
Group 1	42%
Group 2	75%
Group 3	75%
Group 4	85%
Group 5	90%

Table 6: Adverse effect observed in study groups

Side effect	Group 1		2		3		4		5		Total	
	No	%	No	%	No	%	No	%	No	%	No	%
Immediate side effects (within 24 hour)												
None	7	36.84	10	50	5	25	11	52.38	11	55	44	44
Erythema	6	31.57	6	30	5	15	6	28.57	7	35	27	27
Edema	2	10.52	2	10	-	-	-	-	1	5	3	3
Pain	1	5.26	1	5	5	25	1	4.76	1	5	9	9
Pruritus	1	5.26	-	-	5	15	2	9.52	-	-	8	8
Blister	2	10.52	1	5	-	-	1	4.76	-	-	4	4
Total	19	100	20	100	20	100	21	100	20	100	100	100
Remote side effects												
None	13	68.42	-	-	11	55	16	76.19	16	80	56	56
Hyperpigmentation	-	-	-	-	5	25	4	19.04	-	-	9	9
Hypopigmentation	5	26.31	10	50	-	-	-	-	4	20	19	19
Hypopigmentation + atrophy	-	-	4	20	-	-	-	-	-	-	4	4
Hypopigmentation + telangiectacia	-	-	5	25	-	-	-	-	-	-	5	5
Ulcer	1	5.26	1	5	4	20	1	4.76	-	-	7	7
Total	19	100	20	100	20	100	21	100	20	100	100	100

and 5.

Treatment was evaluated by type of response achieved based on improvement in POSAS, side effects observed and recurrence of keloidal lesion 3 months after last treatment session. Group 5 and 4 shows maximum significant improvement(>50% improvement in POSAS) in all parameter ($P<0.05$) with minimal side effect and no recurrence even after 3 months of post treatment showing best result among all groups.

5. Discussion

The study showed faster treatment response with combination therapy. Each of the constituents chosen has a positive effect on reducing the symptoms. When taken together, these constituents minimize the injections sessions required if they were to be administered on an individual basis. Cryotherapy uses refrigerant to cause direct cell and microcirculatory damage causing stasis, thrombosis in blood vessels resulting in tissue necrosis and sloughing followed by tissue flattening.[7,8] There were reports suggest that cryotherapy alter collagen production and induce keloidal fibroblast isolation towards a more normal phenotype. It's supported that the use of cryotherapy just prior to steroid injection in order to induce edema and therefore grease steroid injection and indeed minimize total cure dose. Study of G YOSIPOVICH et al (20) showed treatment with combination of intalesional triamcinolone acetonide and cryotherapy give significantly better result than individual cryotherapy and intralesional triamcinolone acetonide which was also support present trial in which group 2 showed better responses than group 1.

Triamcinolone inhibits the proliferation of normal and keloid fibroblasts, collagen synthesis, increases collagenase production, and reduces levels of collagenase inhibitors. Working through fibroblast glucocorticoid receptors, steroids also induce ultra-structural changes in collagen synthesis that enhance the organization of collagen bundles and degenerate the characteristic keloidal collagen nodules. Triamcinolone acetonide has long been the steroid of choice for the injectional drug in the treatment of hypertrophic scars and keloids. Utmost of the clinical trials in the scar suggests that intralesional corticosteroids, alone, or in combination, give the faster relief of original symptoms as well as leveling of the scars themselves. The use of intralesional corticosteroids has redounded in varying degrees of success, but also has a side effect profile like telangiectasia, skin atrophy, and altered pigmentation.[9] These side effects appeared due to requirement of larger quantities of the drug needed to cure the scar, but with concurrent use of other treatment modalities total cure dose of steroid needed is drop hence lateral effect like skin atrophy, telangiectasia and pigmentory changes can be minimized. Use of steroid plus cryotherapy and steroid plus other intralesional drug like 5 FU and use of silicone gel as adjuvant were observed causing lower side effect as well as duration of treatment time.

Intralesional 5-FU acts by inhibiting fibroblast proliferation and has antimetabolite exertion. It also has an inhibitory effect on TGF-β- induced expression of the type I collagen gene in fibroblasts.[10] It interrupts both DNA and RNA conflation at several situations, including the inhibition of thymidylate synthetase and the production of toxic metabolites. 5FU can be administered

intralesionally in a dose of 50 mg/ mL and has shown favorable results.[10] No systemic complications like anemia, leucopenia, and thrombocytopenia, have been reported following intralesional 5 FU in most of the studies, but adverse effect like pain at injection point, ulceration, burning, and hyperpigmentation were the common locally encountered. .Intralesional 5-fluorouracil into keloids have been shown to be veritably effective in reducing the size of keloids, but are frequently associated with severe pain and conceivably ulceration at the point of injection site. Intralesional TAC causes inhibition of protein formation and fibroblast migration. It also enhances collagen destruction. Steroids are known to inhibit collagen formation and have anti-inflammatory property.

Atrophy, one of the side effect of steroids, is used to achieve desire therapeutic effect in keloids. Addition of 0.1 ml of triamcinolone actinide (40 mg/ ml) to 0.9 ml of 5-FU (50 mg/ ml) help to drop the pain and also the inflammation associated with 5 FU. Systemic absorption followed by intralesional 5 FU has been reported in some study and may cause anemia, leukopenia, and thrombocytopenia.[10] Still, used in combination with other agents enables clinicians to use a lower cure dose and total treatment sessions for each injection, performing in better adequacy with no reported systemic side effects. In this study, pain at the point of injection was a common problem with rules containing 5FU, which is harmonious with other studies.[11–14]

The combination regimen has been proven to be better than TAC alone.[15] A recent meta- analysis by Ren et al.[16] concluded that TAC +5FU is safer and more efficacious than TAC alone.[17] Studies have also shown the effectiveness of the combination to be significantly better than 5FU.[14] Use of silicone gel either as a topical gel or sheet requires covering the entire scar for at least 12 hours each day, and ideally 24 hours per day except when taking bath. Silicone gel presumably acts as an impermeable membrane that keeps the skin moist, performing in a manner similar to the stratum corneum. Silicone gel sheet reduce itching and pain presumably act on mast cell Also improve pliability.[18,19] In addition, all of the patients felt that the skin associated with the scar was softer following silicone gel sheet application, and the injectors noted that posterior injections were "easier" to administer than the first injections. FOTINI et al[20] showed 87% (cases had good to excellent response who was treated with polytherapy same as group 5 and show concordance with result of present study.

6. Conclusion

Combination of different treatment modalities has been shown in this clinical evaluation to be promising and long lasting for the suppression of symptoms related to keloids .In comparison to some surgical procedures and other invasive modalities, this combination therapy is rather inexpensive, easily available, and an effective treatment option that can be offered in the consulting/treatment room

Among all treatment given in this study, (1) cryotherapy with intralesional triamcinolone along with application of silicone gel sheet and (2) cryotherapy with combination of intralesional triamcinolone and 5-Flurouracil show best result with lesser side effect and cosmetically better acceptance.

7. Study limitation

Present study consisted less number of patients in each study group, greater sample size and longer duration of follow up will be required.

8. Conflict of interest

The authors declare they have no conflict of interest.

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