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Comparative study of safety and efficacy of cryotherapy followed by intralesional corticosteroid injection versus intralesional injection of corticosteroid plus 5-flurouracil in the treatment of keloid

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Abstract:

Background: Keloid is an overgrowth of dense, fibrous tissue, usually developing after healing of a skin injury and extends beyond the borders of the original wound. The treatment of keloid has been a challenge, and at times, frustrating because of the recurrence.

Objective: To compare the safety and efficacy of cryotherapy followed by intralesional corticosteroid injection versus intralesional injection of corticosteroid plus 5- flurouracil in the treatment of keloid.

Materials and methods: The Department of Dermatology & Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka conducted a cross-sectional comparative study on 70 outpatients with clinically diagnosed keloids. SPSS 23 was used to analyses data. The significance threshold of $p < 0.05$ was analyzed using the chi-square test and student "t" test. Mean standard deviation was used for continuous scale data and number percentage for categorical data.

Results: Average age was found 33.5±9.3 years in group A, 31.7±10.3 in group B. Scar height was 3.47±0.99 mm in group A and 3.59±0.61 mm in group B. At the first follow-up, scar height was significantly larger in group A (2.54±0.87 vs 2.12±0.54 mm) than group B. At 2nd follow-up, scar height was considerably greater in group A (1.85±1.01 vs 1.10±0.43 mm) than group B Group A had 17 (48.6%) efficacy and group B 26 (74.3The end outcome was good to excellent for 16 (45.7%) in group A and 25 (71.4%) in group B. The two groups showed a significant difference ($p<0.05$). Side effects included 6 (17.1%) skin atrophy in group A but none in B. Telangiectasia was 8(22.9%) in group A and 1(2.9%) in B. Hypopigmentation was 7(20.0%) in group A and absent in B. Ulceration was 47 (11.4%) in group B but not in A. Group A had 14 (40.0%) recurrence and group B 6 (17.1%). The two groups showed a significant difference ($p<0.05$).

Conclusion: Cryotherapy followed by intralesional corticosteroid with 5-fluorouracil treating keloids is more effective, lasts less, and has less side effects than Cryotherapy alone. Cryotherapy followed by intralesional corticosteroid plus 5-fluorouracil reduces scar height considerably.

Keywords: Cryotherapy, Intralesional corticosteroid injection, Intralesional 5-fluorouracil, Keloid treatment, Scar management.

Background

Keloids are abnormal scars that are characterised by nodular lesions that spread beyond the initial injury site and do not naturally go away, typically increasing in size over time [1]. Frequently impacted regions encompass the thorax, deltoids, auricles, and dorsal region, exhibiting symptoms of pruritus and discomfort. Keloids, unlike hypertrophic scars, do not improve with time and often reappear after surgical removal, which can result in cosmetic deformity and functional limitations. Keloid development is caused by an aberrant wound-healing process characterised by an excessive buildup of collagen and a lack of regulatory mechanisms that regulate cell growth and tissue regeneration [3,8,10]. Several treatment methods have been used, such as pressure therapies, silicone gel dressings, injections into the affected area (corticosteroids, 5-FU), radiation, cryotherapy, and laser treatments. However, none of these treatments have been universally effective [4,5,6]. Intralesional cryotherapy is an innovative method that uses freezing to treat scars internally. It has been found to be effective in reducing the volume of scars and alleviating symptoms [7,8]. However, there are worries about the possibility of the scar returning and side effects such as permanent hypopigmentation, especially in patients with darker skin types [9].

Since 1960, intralesional steroid injections have been utilised to treat keloids by diminishing collagen production and fibroblast proliferation [10,13]. Although there are potential negative effects including as atrophy and hypopigmentation, they continue to be widely used as a therapy choice. The combination of steroids and 5-FU has demonstrated efficacy, however it requires repeated therapy sessions and recurrence rates remain elevated [11]. The effectiveness of keloid treatment has been examined through the use of cryotherapy, together with intralesional injections of corticosteroids or 5-FU. Studies indicate that using these combinations yields more favourable outcomes compared to using single therapies. Specifically, the combination of cryotherapy followed by combined corticosteroid and 5-FU injections shows potential for greater results in terms of safety and effectiveness when compared to using cryotherapy followed by corticosteroid injection alone.

Method

The research was carried out in the Department of Dermatology & Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from February to August 2021. The objective was to assess the effectiveness of two treatment protocols for keloids. A total of seventy patients who were clinically diagnosed with keloids were intentionally selected for the study. The inclusion criteria for this study were keloids resulting from trauma, inflammation, or spontaneous causes, a willingness to participate in follow-up, an age range of 10-50 years, and a duration of the keloid lesion of less than five years. The exclusion criteria encompassed pregnancy, lactation, immunosuppressive medication, systemic diseases, contraindications to cryotherapy, substantial burn-related keloids, and non-compliance.

The data collection process included obtaining written consent, gathering demographic information, conducting physical examinations, and doing basic investigations. A conventional survey enabled in-person interviews. Patients who had previously been administered intralesional corticosteroids were required to undergo a three-month period without receiving any further treatment. The participants were categorised into two cohorts: Group A underwent cryotherapy followed by intralesional corticosteroid injections, while Group B underwent cryotherapy followed by intralesional injections of corticosteroid in combination with 5-fluorouracil (5-FU). The treatments were provided every 21 days for a total of three doses. The outcomes were classified into five categories: no improvement, poor (0-25%), fair (25-50%), good (50-75%), and exceptional (75-100%). The data were analysed

using SPSS version 23, utilising chi-square and student's t-tests to determine statistical significance ($p < 0.05$). The continuous data were reported as the mean and standard deviation, whereas the categorical data were provided as numbers and percentages.

The study adhered to ethical protocols, guaranteeing that participants provided informed consent, participated voluntarily, and that their information was kept confidential. Participants were not exposed to any physical, psychological, or social dangers. The researcher collected data in order to minimise errors, and a pretest was conducted to improve the data collection method. Adherence to the Helsinki Declaration for Medical Research Involving Human Subjects was guaranteed, ensuring the protection of privacy and confidentiality, as well as providing participants with the option to withdraw at any point.

Results

The objective of the study was to assess the safety and effectiveness of two treatment protocols: cryotherapy followed by intralesional corticosteroid (Group A) and cryotherapy followed by intralesional corticosteroid in combination with 5-fluorouracil (Group B). Patients had a treatment regimen spanning three months, with a gap of 21 days between each dose. The eligibility criteria were individuals aged between 10 and 50 years, with keloids arising from trauma, inflammation, or spontaneous sources, and a lesion duration of less than five years. The exclusion criteria encompassed pregnancy, lactation, systemic diseases, and contraindications to cryotherapy.

Table 1: Socio-demographic characteristics of the study patients (n=70)

Parameters	Group A (n=35)		Group B (n=35)		P value
	n	%	n	%	
Age (years)					
≤20	4	11.4	6	17.1	
21-30	9	25.7	11	31.4	
31-40	17	48.6	14	40.0	
41-50	5	14.3	4	11.4	
Mean±SD	33.5±9.3		31.7±10.3		0.445^{ns}
Sex					
Male	16	45.7	14	40.0	0.629^{ns}
Female	19	54.3	21	60.0	
Socio-economic status					
Lower middle	5	14.3	3	8.6	
Middle	28	80.0	31	88.6	0.610^{ns}
Upper middle	2	5.7	1	2.9	

The socio-demographic study revealed no statistically significant disparities between the two groups in terms of age, gender, or socio-economic level. The majority of patients were within the age range of 31-40 years, with females being the main gender in both categories. The bulk originated from families with moderate incomes. Likewise, there was no significant difference in the duration of lesions across the groups. Initially, the average scar height was similar in both groups. However, throughout the first and second follow-ups, Group B exhibited much more pronounced decreases in scar height compared to Group A.

Table 2: Duration of lesion of the study patients (n=70)

Duration (years)	**Group A (n=35)**		**Group B (n=35)**		**P value**
	n	**%**	**n**	**%**	
<1	3	8.6	5	14.3	
1-3	15	42.9	18	51.4	0.441[ns]
4-5	17	48.6	12	34.3	

ns=not significant
P value reached from Chi square test

Both patient and observer evaluations suggested that Group B achieved superior outcomes, with a greater proportion of results rated as good to excellent. More precisely, 65.71% of patients in Group B indicated positive outcomes, while just 40% of patients in Group A stated the same. Observer evaluations corroborated these results, indicating that Group B exhibited much greater favourable outcomes (62.86%) in comparison to Group A (34.29%).

Table 3: Comparison of Patient and Observer assessment scale between treatment groups (n=70)

	Group A (n=35)		**Group B (n=35)**		**P value**
	n	**%**	**n**	**%**	
Patient assessment scale					
No improvement	1	2.86	0	0.00	0.13[ns]
Poor (0-25%)	3	8.57	0	0.00	
Fair (25-50%)	12	34.29	8	22.86	
Good (50-75%)	14	40.00	23	65.71	
Excellent (75-100%)	05	14.29	04	11.43	
Observer assessment scale					
No improvement	1	2.86	0	0.00	0.03[s]

Poor (0-25%)	5	14.29	0	0.00	
Fair (25-50%)	13	37.14	8	22.86	
Good (50-75%)	12	34.29	22	62.86	
Excellent (75-100%)	04	11.43	05	14.29	

s=significant; ns=not significant

P value reached from Chi square test

No improvement
Poor (0-25%)
Fair (25-50%)
Good (50-75%)

In addition, Group B experienced a much lower number of adverse effects, including no instances of skin shrinkage or hypopigmentation, and fewer recurrences compared to Group A. Group B was the only group in which ulceration and hyperpigmentation were detected. The study found that the combined treatment of cryotherapy and intralesional corticosteroid + 5- fluorouracil was superior in efficacy and had fewer adverse effects compared to cryotherapy followed by intralesional corticosteroid alone.

Table 4: Comparison of side effects between treatment groups (n=70)

Side effects	**Group A (n=35)**		**Group B (n=35)**		**P value**
	n	**%**	**n**	**%**	
Skin atrophy	6	17.1	0	0.0	0.010[s]
Telangiectasia's	8	22.9	1	2.9	0.012[s]
Hypopigmentation	7	20.0	0	0.0	0.005[s]
Ulceration	0	0.0	4	11.4	0.039[s]
Hyperpigmentation	0	0.0	3	8.6	0.076[ns]
Recurrence	14	40.0	6	17.1	0.034[s]

Discussion

This study, conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka, aimed to evaluate the safety and efficacy of two treatment protocols for keloids: cryotherapy followed by intralesional corticosteroid (Group A) and cryotherapy followed by intralesional corticosteroid plus 5-fluorouracil (Group B). The study had a total of 70 individuals, with the majority falling within the age range of 31-40 years. There were no significant differences in age or gender among the various groups. Most patients came from households with moderate earnings. The effectiveness of the treatment was assessed by measuring the decrease in scar height and by performing evaluations from both the patients and observers over a period of three months [14]. Group B had a significantly greater reduction in scar height during the follow-up periods in comparison to Group A, indicating a more effective response to the combined treatment of corticosteroid and 5-fluorouracil. These findings are consistent with the studies carried out by Khalid et al. [14], Kaushal et al. [15], and Saleem et al. [16].

After doing patient assessments, it was determined that 65.71% of persons in Group B had good outcomes, but only 40% of individuals in Group A stated the same. Nevertheless, it is crucial to acknowledge that the observed disparity between the two groups did not reach statistical significance. Observer assessments showed a significant difference, with 62.86% of persons in Group B achieving favourable findings compared to only 34.29% in Group A. Group B exhibited a superior proportion of outstanding to exceptional performances (71.4%) in contrast to Group A (45.7%) in the final results. Khalid et al. [14] and Nanda and Reddy [17] reported similar findings, emphasising the enhanced efficacy of the combined therapy. Group B had a significant decrease in side effects, with no occurrences of skin atrophy or hypopigmentation, and lower rates of recurrence compared to Group A. These findings are consistent with the previous studies conducted by Asilian et al. [18] and Darougheh et al. [19].

Group A demonstrated higher rates of skin shrinkage (17.1%), telangiectasia (22.9%), and hypopigmentation (20%), whereas Group B had lower occurrences of ulceration (11.4%) and hyperpigmentation (8.6%). Khalid et al. [14] and Manuskiatti and Fitzpatrick [20] reported increased rates of problems in the group that received just corticosteroids. The study's results indicate that the use of both intralesional corticosteroid and 5-fluorouracil is a better therapy choice for keloids. This treatment option provides enhanced effectiveness, decreased adverse effects, and lower chances of the keloids coming back. The study is constrained by its exclusive focus on one centre and its restricted number of participants. This highlights the need for larger, multicenter trials to confirm these findings and prove the long-term benefits of this therapeutic approach.

Conclusion

The combination of Cryotherapy followed by intralesional injection of corticosteroid + 5-fluorouracil is a more successful treatment for keloids compared to Cryotherapy followed by intralesional corticosteroid alone. This treatment approach results in good and excellent outcomes, with shorter duration and fewer side effects. The use of combination cryotherapy followed by intralesional injection of corticosteroid plus 5 fluorouracil is strongly advised for the treatment of keloid.

Conflict of interest: No

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