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Effectiveness of Combination Use of Intralesional Steroid with 5-fluorouracil in The Treatment of Keloid Patients

*AK Basak[1], J Debnath[2], MM Hossain[3], MA Hasanat[4]

Abstract

Background: Keloids are a common problem with significant recurrence rates despite intralesional steroid treatment and 5-fluorouracil in combination with triamcinolone may be superior to triamcinolone alone. **Objectives:** To evaluate the effectiveness of the combination use of intralesional steroids with 5-fluorouracil in the treatment of keloid. **Methods:** The study was a descriptive cross-sectional study and was conducted at the Department of Dermatology and Venereology, Khwaja Yunus Ali Medical College (KYAMC), Enayetpur, Sirajganj, from July 2020 to June 2021. A total of 100 patients with keloid were included in this study. These patients were subjected to history, clinical examination, and investigations. In all cases, informed written consent was taken from the Participants and a separate case record form was used during data collection. Collected data were analyzed by the statistical software IBM SPSS 25. **Results:** This study shows that the majority (68%) of patients belonged to the age group of 21-30 years. The mean age was 26.43±7.77 years. Regarding sex, 56% were females and 44% were males with a male-female ratio of 1.3:1. 52% of patients had a duration of lesion up to 1 year, 22% of patients had 1-2 years and 26% of patients had >2 years. The most common site of keloid was the chest (38%), then face (32%), upper extremity (16%), shoulder (6%), back (4%). The most common presenting symptoms were pruritis (56%), then 38% were cosmetic disfigurement, 32% were skin discoloration, 28% were pain and 18% were restriction of movement. Trauma was the commonest factor seen in 34% of the patients followed by ear piercing (22%) and infection (20%). Other causes were spontaneous (10%), acne (6%), burns (6%), and post-surgical keloid (2%). 16 had a positive family history of the keloid disease. The majority (70%) had good outcomes followed by excellent outcomes in 22% and 8% had average outcomes. It was observed that most patients (88%) did not have any adverse effects. Only 12% had adverse effects seen as skin ulceration (6%), skin atrophy (4%) and telangiectasia (2%). **Conclusion:** This study revealed that the combination use of intralesional steroids with 5-fluorouracil in the treatment of keloid seems to offer the balanced benefit of faster and more efficacious response with fewer adverse effects. Treatment has to be individualized and can be combined with one or more modalities to aim for better efficacy and safety.

Keywords: Steroid, 5-fluorouracil, Keloid.

1. Dr. Arpan Kumar Basak, Associate Professor, Department of Dermatology, Khwaja Yunus Ali Medical College, Sirajganj, Bangladesh. Email: arpanbasak2010@gmail.com
2. Dr. Joya Debnath, Associate Professor, Department of Forensic Medicine, Kumudini Women's Medical College, Tangail, Bangladesh.
3. Dr. Md. Munjur Hossain, Associate Professor, Department of Anaesthesiology, Ad-din Akij Medical College, Khulna, Bangladesh.
4. Dr. Md. Abul Hasanat, Associate Professor & Head, Department of Physiology, Gazi Medical College, Khulna, Bangladesh.

Introduction

Keloids are characterized by firm, mildly tender, bosselated nodules or plaques occurring more frequently on shoulders, chest, neck, upper arms and face.[1] They are a benign overgrowth of fibrous tissue that usually develops after the healing of a skin injury and extends beyond the original defect.[2] The uncontrolled growth of keloid continues progressively, and the patients experience itch and pain. The fibrous keloid progresses to gain a larger size, leads to cosmetic disfigurement, and functional impairment, and affects the quality of life adversely.1 The incidence of keloids is reported to be 4.5% to 16% in darker-skinned individuals.[3]

Keloids are frequently symptomatic, with most patients reporting tenderness or pruritis. Keloids occur most commonly on the chest, shoulders, upper back, back of the neck and earlobes.[4,5] Female predominance has been noted but this may, in part, be reflected by the number of ear lobe keloids secondary to piercing among women.[6] Unusual cases of massive keloids have been reported following severe burn injuries and at the sites of vaccination.[7,8] Genital keloids have been reported to occur after circumcision or following trauma.[9] In addition, multiple cases of cornea keloids following corneal trauma have been described.[10] Keloids usually occur after trauma or wounding of the skin. Keloidal scars typically extend beyond the original wound and spread by invasion rather than expansion.[11] Patients with the highest risk of developing keloids are between the ages of 10 to 25 years. In addition to cosmetic disfigurement, keloids may cause protracted itch and pain.[12] On histologic examination, keloids are found to have increased collagen and glycosaminoglycan deposition, both major components of the extracellular matrix.[13] The collagen in keloids consists of thickened whorls of hyalinized collagen bundles in a haphazard array, known as keloidal collagen.[14] This is in contrast to normal scars where collagen bundles are oriented parallel to the skin surface.[15] Clinicians always find it difficult to treat hypertrophic scars and keloids.[16]

Traditionally, intralesional triamcinolone has been the mainstay of keloid treatment, in conjunction with re-excision and adjuvant therapies such as radiation and compression.[3] Intralesional steroid injection combined with excision has resulted in efficacy rates ranging from 58% to 93% in several studies.[17-19]

Triamcinolone acetonide (TAC) is the most commonly used intralesional corticosteroid for the treatment of keloids and is considered to be the first-line therapy for the treatment of keloids.[1] TAC is used in different concentrations ranging from 10 to 40mg/ml. Different studies recommend different intervals between successive injections and the number of injections may vary from four to eight.[1]

Intralesional injection TAC 40mg/ml is more commonly used, as the concentration of 40mg/ml is very effective in controlling keloid. However Local side effects such as dermal atrophy, telangiectasia, hypopigmentation and pain at the site of injection due to TAC 40mg/ml are common. Pain can be avoided by the use of topical anesthesia and/or regional injections of local anesthetic around the scars.[1]

Intralesional 5-fluorouracil (5-FU) has been tried in hypertrophic scars and keloids in combination or as an individual therapeutic agent.[20] This study aimed to determine the safety and efficacy of the combination use of intralesional steroids with 5-fluorouracil in the treatment of keloid.

Materials & methods

It was a cross-sectional study carried out in the Department of Dermatology and Venereology, KYAMC, Enayetpur, Sirajganj from July 2020 to June 2021. A total of 100 patients with keloid were included. Baseline assessment was made by taking photographs, palpating for the firmness of lesions and measuring the size using a Verniers caliper. The patients received a combination of intralesional steroid with 5-fluorouracil for at least 3 sessions spaced 4 weeks apart.

The combination use of intralesional steroid with

5-fluorouracil protocol was as follows: triamcinolone acetonide 40mg/mg and 5-fluorouracil 50mg/ml were used. A mixture of 75% 5-FU and 25% triamcinolone acetonide was used; 0.1 ml of solution per centimeter of the lesion was injected. The corticosteroid was injected directly into the keloid with a 30 gauge needle attached to a 1 ml insulin syringe. The volume injected differed among the patients due to varying sizes of the keloids and ranged between 0.1ml- 0.5ml.

To evaluate the treatment outcome, improvement was graded as excellent, good, average, and poor; depending upon the percentage of flattening. **Poor:** No improvement/<25% flattening, **Average:** 25-49% flattening, **Good:** 50-74% flattening, **Excellent:** ≥75% flattening. Patients' satisfaction scale was used to evaluate the treatment outcome at completion of six treatment sessions: 0: Static/no improvement, 1: Slight improvement, 2: Marked improvement, 3: Excellent improvement/complete flattening. Data was processed and analyzed using computer software SPSS (Statistical Package for Social Sciences) for Microsoft Windows version 25.

Results

Table 01: Demographic characteristics of the study subjects (n=100)

Age in years	Frequency	Percentage (%)
11-20	14	14
21-30	68	68
31-40	12	12
41-50	6	6
Mean±SD	26.43±7.77	
Sex		
Male	44	44
Female	56	56

Table 02: Duration of lesion of the study subjects (n=100)

Duration of lesion	Frequency	Percentage (%)
Upto 1 year	52	52
1-2 year	22	22
>2 years	26	26

Table 03: Site of lesion of the study subjects (n=100)

Site	Frequency	Percentage (%)
Back	4	4
Chest	38	38
Face	32	32
Lower extremity (leg)	4	4
Shoulder	6	6
Upper extremity (arm, forearm, hand)	16	16

Table 04: Presenting symptoms and signs of the study subjects (n=100)

Symptoms & signs	Frequency	Percentage (%)
Pruritis	56	56
Pain	28	28
Cosmetic disfigurement	38	38
Skin discoloration	32	32
Restriction of movement	18	18

Table 05: Predisposing factor of the study subjects (n=100)

Predisposing factor	Frequency	Percentage (%)
Acne	6	6
Burn	6	6
Ear piercing	22	22
Infection	20	20
Post-surgical	2	2
Spontaneous	10	10
Trauma	34	34

Table 06: Outcome of the treatment of the study subjects (n=100)

Grade of improvement	Frequency	Percentage (%)
Poor (no improvement/ <25% flattening)	00	00
Average (25-49% flattening)	8	8
Good (50-75% flattening)	70	70
Excellent (≥ 75% flattening	22	22

Table 07: Adverse effects observed in the study subjects (n=100)

Adverse effects	Frequency	Percentage (%)
Telangiectasia	2	2
Skin atrophy	4	4
Skin ulceration	6	6

Discussion

Keloids are a common and difficult problem to treat. Keloids are a common problem with significant recurrence rates despite intralesional steroid treatment and multimodal therapy. A wide variety of modalities have been used to treat keloids, reflecting a lack of consensus on an ideal regimen. Many modalities of keloid treatment have been advocated which have a variable and transient success.[21-24] There is no universally accepted treatment resulting in a permanent cure. Hence there is a need for evaluation of better modalities to achieve good cosmetic acceptability. A hospital-based clinical trial was carried out to determine the safety and efficacy of the combination use of intralesional steroids with 5-fluorouracil in the treatment of keloid. The present study findings were discussed and compared with previously published relevant studies.

In this study 68% of patients belonged to the age group of 21-30 years followed by followed by 14% were 11-20 years, 12% were 31-40 years and only 6% were 41-50 years. The average age was 26.43±7.77 years. In previous studies, Garg et al.[1] the onset of keloid was seen most commonly between 10 and 30 years. A similar study by Davison et al.24 found that keloid usually occurs in young age group. 88% of the lesions occur in patients <30 years of age group because youngsters are frequently subjected to trauma. Another study found the average age was 22.6 years.[2]

Regarding sex out of 60 patients, 56% patients were female and 44% patients were male with a male-female ratio of 1.3:1. This is per earlier studies by Muneuchi et al.[17] and Srivastava et al.[19], Adit et al.[25] found almost equal incidence among both males and females.

This study shows that 52% of patients had a duration of lesion up to 1 year, 22% of patients were 1-2 years and 26% of patients were >2 years. Clemens et al.[3] in their study observed that most of the keloids occur within 1 year of local trauma and others as early as 2-4 weeks. Khan et al.[26] study found that majority of the patients the duration of keloid was 3-6 months. In this present study, the longer duration of the lesion can be attributed to the negligence on the part of the patients.

In this study, the most common site of keloid was the chest (38%), then the face (32%), upper extremity (16%), shoulder (6%), and back (4%). Although keloids may be found anywhere on the body, they are found to have regional predilection, occurring most often on the ear, anterior chest, upper back, and shoulders.[2] According to Garg et al.[1] study the most frequently involved sites for the keloids are the chest, shoulders, head-neck areas (especially ear lobes), arms and upper back. Srivastava et al[19] found a higher incidence of keloids over the presternal area followed by the

deltoid and ear. Vidhi et al.[27] found that keloids occur most commonly on the chest, shoulder, upper back, nape of the neck and ear lobes.

In current study shows the most common presenting symptoms were pruritis (56%) then 38% were cosmetic disfigurement, 32% were skin discoloration, 28% were pain and 18% were restriction of movement. Therefore, the findings of the study are in good agreement with the findings of the other research works.[18,19,23,26] According to Shivaswamy et al.[2] keloid lesions are usually asymptomatic but may be tender, painful, or pruritis or may cause a burning sensation.

This study shows trauma was the commonest factor seen in 34% of the patients followed by ear piercing (22%) and infection (20%). Other causes were spontaneous (10%), acne (6%), burns (6%) and post-surgical keloid (2%). Factors such as trauma, tension and hormones have been associated with keloid formation. Trauma is the most frequently associated factor according to the study of Srivastava et al.[19] Many theories have been advanced to explain the etiology of keloid. In most patients, trauma was the major provoking factor.[2,17,22,23] Infection has been also incriminated as a contributing factor in the formation of keloid in Kelly's study.[2] Even though some individuals may report spontaneous keloid formation, it may be that the initial skin wound that incited its development has been forgotten.[21]

This study shows that 8% had a positive family history of keloid disease. A similar study by Garg et al.[1] study reported a familial incidence of 4.5%-16% in the black and Hispanic population. A family history of keloid is frequently elicited in the study of Nagarur et al.[22] In familial cases the exact mode of inheritance is unclear, with both autosomal recessive[23] and autosomal dominant[27] pattern of inheritance being reported.

In the present study, the majority (70%) were good outcomes followed by 22% were excellent outcomes and 8% were average outcomes. Therefore, the findings of the study are in good agreement with the findings of the other research works (Nagarur et al.).[22] They found out of 33 patients, 24 (73)% showed good response followed by excellent response in 7 (21%) patients, fair response in 2 (6%) patients, and no patients showed poor response. In another study majority of patients i.e., 71.4% of patients showed good response, followed by 14.3% fair response, 7.1% excellent response and 7.1% patients showed poor response.[26] The symptoms disappeared in 17 (70.8%) patients and improved in 3 (12.5%) patients.[27] Kontochristopoulos et al. found that out of 20 patients, 17 (85%) patients showed more than 50% improvement.[28]

This study found combination use of intralesional steroid with 5-fluorouracil in the treatment of keloid are all effective in keloid disease. A combination of intralesional steroid with 5-fluorouracil seems to offer the balanced benefit of faster and more efficacious response. These findings are consistent with the study of Srivastava et al.[19] and Nagarur et al.[22]

In this study, it was observed that out of 60 patients (88%) did not have any adverse effects. Only (12%) found adverse effects seen in skin ulceration (6%), skin atrophy (4%) and telangiectasia (4%). In previous studies by Davison et al.[24] and Nanda et al.[28] regarding the incidence of adverse effects, there was no statistically significant difference between the 5-FU and steroid-only groups. However, one could speculate the telangiectasias in the 5-FU group were likely caused by the steroid component.

Conclusion

This study shows a combination of Intralesional steroid with 5 - fluorouracil was the more

effective treatment of keloid disease and faster response with fewer adverse effects. Treatment has to be individualized and can be combined with one or more modalities to aim for better efficacy and safety. Long-term prospective randomized studies are needed in the area of keloid treatment.

References

1. Garg AM, Shah YM, Garg A, Zaidi S, Saxena K, Gupta K, Ramya BG. The efficacy of intralesional triamcinolone acetonide (20mg/ml) in the treatment of keloid. Int Surg J. 2018;5(3):868-872

2. Burrows NP, Lovell CR. Disorders of Connective Tissue. In: Burns T, Rook A. Rooks textbook of dermatology. 8th Ed. Oxford: Wiley-Blackwell; 2010:45.54-45,56.

3. Clemens, MD; Smitha Sonni, MD; Antai Wang, PhD; and Amy Crane, MD. Efficacy of Intralesional 5-Fluorouracil and Triamcinolone in the Treatment of Keloids. (Aesthetic Surg J 2009;29:40–46.

4. Prabhu A, Sreekar H, Powar R, Uppin VM. A randomized controlled trial comparing the efficacy of intralesional 5-fluorouracil versus triamcinolone acetonide in the treatment of keloids. J Sd S.oc. 2012.39:19-25

5. Mutalik S. Treatment of keloids and hypertrophic scars. ipdian J Dermatol Venereol Leprol. 2005 Jan-Feb; 71(1):3-8.

6. Maguire HC. Treatment of keloids with triamcinolone acetonide injected intralesionally. JAMAl 965;l 92:325-6.

7. Gupta S. Sharma VK. Standard guidelines of care: Keloids and hypertrophic scars. Indian J Dermatol Venere Leprol 2011:77:94-100.

8. Al-Attar A. Mess S. Thomassen JM, Kauffman CL, Davison SP. Keloid pathogenesis and treatment. Plas Recoristr Surg 2006;117:286-300.

9. Zouboulis CC. Blume U, Buttner P, Orfanos CE. Outcomes of cryosurgery in keloids and hypertrophic scars. A perspective consecutive trial of case series. Arch Dermatol 1993;129:1146-51.

10. Douglas L. Maxwell F, David R. Treatment of Keloids and Hypertrophic Scars: A Meta-analysis and of the Literature. Arch Facial Plast Surg. 2006;8(6):362-368.

11. Shepherd JP, Dawber RP. The response of keloid scars to cryosurgery. Plast Reconstr Surg 1982:70-81.

12. Zoubouls CC. Principles of cutaneous cryosurgery: An update. Dermatology 1999;198:111-7.

13. Rusciani L, Rossi G, Bono R. Use of cryotherapy in the treatment of keloids. J Dermatol Surg OncoII 1993:19:529-34.

14. Gupta S. Kumar B. Intralesional cryosurgery using lumbar puncture and/or hypodermic needles for large, bulky. recalcitrant keloids. Int J Dermatol 2001;40:349-53.

15. Hirshowitz B, Lerner D, Moscana AR. Treatment of keloid scars by combined cryosurgery and intralesional corticosteroids. Aesth Plast Surg 1982;6:153-8.

16. Alster TS. Tanzi EL. Hypertrophic scars and keloids etiology and management. Am J Clin Dermatol 2003:4:35-43.

17. Muneuchi G, Suzuki S, Onodera M, Ito O, Hata Y, Igawa HH. Long-term outcome of intralesional injection of triamcinolone acetonide for the treatment of keloid scars in Asian patients. Scand J Plast Reconstr Surg Hand Surg 2006;40:111–116.

18. Tang YW. Intra- and postoperative steroid injections for keloids and hypertrophic scars. Br J Plast Surg 1992;45:371–373.

19. Srivastava S, Patil A, Prakash C, Kumari H. Comparison of Intralesional Triamcinolone Acetonide, 5-Fluorouracil, and Their Combination in Treatment of Keloids. World J Plast Surg 2018;7(2):212-219.

20. Hatamipour E, Mehrabi S, Hatamipour M, Shirazi HRG. Effects of Combined Intralesional 5-Fluorouracil and Topical Silicone in Prevention of Keloids: A Double-Blind Randomized Clinical Trial Study. Acta Medica Iranica 2011; 49(3): 127-130.

21. Shivaswamy KN, Shyamprasad AL, Sumathy TK, Suparna MY. Clinical Efficacy of Low Dose Intralesional 5-Fluorouracil (5-FU) in the Treatment of Keloids. Journal of Evolution of Medical and Dental Sciences 2015;4(Issue 97): 16229-16231.

22. Nagarur K, Raja NR. A comparative study between intralesional 5-fluorouracil combined with triamcinolone acetonide and triamcinolone acetonide alone in the treatment of keloids. Int J Basic Clin Pharmacol. 2016;5(3):1090-1098.

23. Gupta S, Kalra A. Efficacy and Safety of Intralesional 5-Fluorouracil in the Treatment of Keloids. Dermatology 2002;204:130–132.

24. Davison SP, Dayan JH, Clemens MW, Sonni S, Wang A, Crane A. Efficacy of Intralesional 5-Fluorouracil and Triamcinolone in the Treatment of Keloids. Aesthetic Surg J 2009;29:40–46.

25. Kontochristopoulos G, Stefanaki C, Panagiotopoulos A, Stefanaki K, Argyrakos T, Petridis A, et al. Intralesional 5-fluorouracil in the treatment of keloids: an open clinical and histopathologic study. J Am Acad Dermatol. 2005;52:474-9.

26. Khan MA, Bashir MM, Khan FA. Intralesional triamcinolone alone and in combination with 5-fluorouracil for the treatment of Keloid and Hypertrophic scars. JPMA 2014; 64:1003.

27. Shah VV. Aldahan AS, Mlacker S, Alsaidan M, Samarkandy S, Nouri K. 5-Fluorouracil in the Treatment of Keloids and Hypertrophic Scars: A Comprehensive Review of the Literature. Dermatol Ther (Heidelb) 2016; 6:169–183

28. Nanda S, Reddy BS. Intralesional 5-fluorouracil as a treatment modality of keloids. Dermatol Surg. 2004;30:56-7.