e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 14 (1); 119-125

Original Research Article

Study of Clinical Response between Treatment of Keloids with Intralesional Injection of Bleomycin plus Triamcinolone Acetonide versus Intralesional Cryotherapy plus Triamcinolone Acetonide

Manohari Tushar[1], Pati Sandhyarani[2], Subudhi S Jaganath[3], Rout Kumar Suresh[4], Ram Kumar Manoj[5], Mohanty Prasenjeet[6], Bisoyi Diptiranjani[7*], Mohanty Jayashree[8]

[1]Senior Resident, Dept. of Dermatology, Jajati Keshari MCH, Jajpur, Odisha
[2]Assistant Professor, Dept. of Medicine, MKCG MCH, Berhampur, Odisha
[3]Assistant Professor, Dept. of Surgery, MKCG MCH, Berhampur, Odisha
[4]Assistant Professor, Dept. of Radiotherapy, VIMSAR, Burla, Odisha
[5]Assistant Surgeon, Dept. of Dermatology, SCB MCH, Cuttack, Odisha
[6]Professor, Dept. of Dermatology, SCB MCH, Cuttack, Odisha
[7]Assistant Professor, Dept. Of Dermatology, SCB MCH, Cuttack, Odisha
[8]Professor, Dept. of Dermatology, SCB MCH, Cuttack, Odisha

Received: 18-10-2023 / Revised: 21-11-2023 / Accepted: 26-12-2023
Corresponding author: Dr Bisoyi Diptiranjani
Conflict of interest: Nil

Abstract:

Introduction: Keloids are an unusual pathological reaction to skin damage in which the tissue of the wound expands excessively beyond the initial cause of the lesion. These are benign non-cancerous fibro proliferative skin growths that occur when there is an excessive development of bigger, thicker, and more irregularly arranged collagen near the site of a previous skin injury. Frequent factors encompass surgical procedures, immunisation, thermal injuries, ear piercing, and acne. Bleomycin is a glycopeptide antibiotic commonly employed as an anti-cancer medication. It triggers programmed cell death in endothelial cells and hampers the production of collagen by blocking the lysyl-oxidase enzyme and TGFβ. In 1996, Bodokh and Brun were the first to utilise it in the treatment of keloids. The medications can have a synergistic impact when administered together.

Objectives:

1. To compare the efficacy of both the procedures.
2. To achieve minimum recurrence and side effects.

Methodology: After obtaining ethical clearance and written informed consent, this study was done among 50 patients with keloid/s, both male and female attending the dermatology OPD in a tertiary health care centre and not received any kind of treatment or intervention before commencement of this study. Skin test with lignocaine was done using 0.1ml of 2% lignocaine solution to see for any hypersensitivity in both the groups. After surgical cleaning of the site, 2% lignocaine was administered as field block in both the groups.

Results: In our study the prevalence of keloids was found to be more among males as compared to females. The majority of keloids were seen in the 16 to 35 years of age group in our study. About 56% patients had keloids of <5 year Duration. Family history of keloid was present in 10% of Patients. Pruritus was the most common presenting symptoms seen in 74% cases, followed by cosmetic and pain. In Group A pain was the most common early side effect, But in Group B all other early side effects like ulceration, bulla formation and secondary infection was more common. Delayed Side effects like hyperpigmentation, atrophy and telamgiectasia were slightly common in Group A as compared to Group B probably because of more no of steroid doses. But hypopigmentation was common in Group B.

Conclusion: Our study concludes that combination therapies should be the preferred modalities of treatment in keloids rather than monotherapies. Both the treatment options showed promising result. Tramcinolone plus Bleomycin was found to be slightly better in terms of efficacy as compared to crytherapy plus tramcinolone.

Keywords: Keloids, Intralesional injection, Bleomycin, Cryotherapy, Side effects.

Introduction

The word keloid is derived from the Greek word chele, or crab's claw. [1] Keloids are an abnormal pathological reaction to skin damage in individuals who are genetically susceptible, characterised by the

excessive growth of wound tissue beyond the original injury site. These are benign non-cancerous fibro proliferative skin growths that occur when there is an excessive creation of bigger, thicker, more irregularly shaped collagen near the location of a previous skin injury. [2,3] Frequent causes encompass surgical procedures, immunisation, thermal injuries, earlobe piercing, and acne outbreaks. These lesions primarily impact people with darker skin tones, particularly those of African, Asian, and Hispanic descent. [4] Keloids can result in both cosmetic deformities and symptomatic problems, often leading to itching, pain, and a reduced quality of life. Due to the lack of clear aetiology, the treatment of keloids remains a longstanding difficulty, and a globally successful therapy has not yet been demonstrated.

In Japan, steroid impregnated tape is the preferred first therapy, but in the USA, steroid (triamcinolone acetonide) injections are the preferred treatment option. [5,6] Additional conventional therapies comprise the use of silicone sheets, compression, intralesional administration of 5-fluorouracil, bleomycin, verapamil, hyaluronic acid and hyaluronidase, botulinum toxin, and collagenase, cryotherapy, laser, radiofrequency ablation, radiation, extracorporeal shockwave therapy, pentoxifylline, and the application of dupilumab and excision. [7,8]

Currently, combined therapy is being employed to achieve improved outcomes and reduce the likelihood of recurrence. Intralesional corticosteroids are the primary therapy for keloids. Corticosteroids diminish the growth of keloids by inhibiting the production of collagen and glycosaminoglycans, as well as limiting the activity of fibroblasts. This effectively hampers the inflammatory response and cell division process.

Bleomycin is a glycopeptide antibiotic often employed as an anticancer drug. It triggers programmed cell death in endothelial cells and hampers the production of collagen by blocking the activity of the lysyl-oxidase enzyme and TGFβ. Bodokh and Brun initially employed it in the treatment of keloids in 1996. The medications can have a synergistic impact when administered together. [9,10,11] Intralesional cryotherapy is a therapeutic technique that involves freezing scar tissue from inside. [12,13] Intralesional probe is used to destroy scar tissue by creating ice crystals within the cells and depriving them of oxygen. The freezing temperature disrupts the connections between endothelial cells, leading to blood stagnation, vascular injury, and tissue death. Currently, the preference is for the combination of two medicines rather than monotherapy. [14]

Until now, there have been few studies comparing the effectiveness of intralesional Bleomycin and Tramcinolone with Cryotherapy (topical) with Tramcinolone in treating keloids. [15,16] Therefore, our objective is to conduct a comparative analysis of the effectiveness of Bleomycin and cryotherapy, both of which will be used in conjunction with Tramcinolone.

Objectives:

- To compare the efficacy of both the procedures.
- To achieve minimum recurrence and side effects.

Material and Methods:

This randomized open level prospective study was done among the 50 patients with keloid/s, both male and female attending the dermatology OPD at SCB Medical College, Cuttack from March 2021 to September 2022.

Inclusion criteria:

All the patients with keloid/s attending SKIN & VD OPD, Not received any kind of treatment or intervention before commencement of this study.

Exclusion criteria:

Patients with history of coagulopathies, cardiac diseases, severe systemic disorders and malignancy, patients under 12 yrs age, females with a history of pregnancy/lactation in last 12 months, patients who were not willing for follow up after initial visit and unusually high expectation, and had large keloids (> 10 cm) were excluded from the study.

Methodology:

Study were started after obtaining ethical clearance and written informed consent. Thorough history of each patient was taken, clinical examination and baseline investigation was done, and photographs were also taken prior to the treatment. Patients meeting the inclusion criteria were randomly selected by computerized random no allocation for I/L triamcinolone acetonide plus I/L bleomycin & I/L cryotherapy plus I/L triamcinolone acetonide as group-A and group-B. Skin test with lignocaine was done using 0.1ml of 2% lignocaine solution to see for any hypersensitivity in both the groups. After surgical cleaning of the site, 2% lignocaine was administered as field block in both the groups. In group-A after giving Local anaesthesia 0.1 ml of 40 mg/ml Triamcinolone and bleomycin at a concentration of 1.5 IU/ml 0.1 ml was given i.e. 0,378 IU/cm2 apart with the help of insulin syringe at an of 30-45 degree. Aspiration was done to check whether the needle was in a blood vessel and in the group-B intralesional cryotherapy was given after giving Local anaesthesia Followed by with 0.1 ml of 40 mg/ml I/L triamcinolone acetonide 40 mg/ mL 1cm2 apart was injected intralesionally using insulin syringe in the next month follow up visits.

For giving intralesional cryotherapy a cryogun, an i.v set and a 18 gauge needle were uses. Liquid nitrogen was used as the cryotherapy agent. The needle was inserted through the long axis of the lesion till the tip appears on other side. It was attached to the I.V set. Cotton pads were given on both the sides to avoid peripheral tissue damage.

Other end of the I.V set was cut and was subsequently attached to the tip of the cryogun and liquid nitrogen was passed through it till complete frosting appeared on the lesion. Two freeze thaw cycles were given. The clinical assessment of scar was done based on the patient and observer scar assessment scale and Vancouver scar scale.

Statistical analysis: Data was entered in Microsoft Excel Spread sheet and analyzed. Significance values were analyzed using standard SPSS software. Comparison of data between the two groups was done.

Categorical data analysis was done using intention to treat (ITT) and per protocol analysis between two groups. P-value of 0.05 or less was considered statistically significant.

Observation and Results:

Out of 50 patients 25 patients (group-A) receiving intralesional triamcinolone plus bleomycin and 25 patients (group-B) intralesional cryotherapy plus triamcinolone were observed and the results were tabulated and analyzed statistically.

Table 1: Age and sex wise distribution

Age group	Group-A		Group-B		P value
	n	%	N	%	
≤ 15	3	12	2	8	0.514
16-25	10	40	11	44	
26-35	8	32	10	40	
36-45	4	16	1	4	
>45	0	0	1	1	
Total	25	100	25	100	
Gender	13	52	14	56	0.777
	52	48	11	44	

Majority of patients in this study were in age group 16-25 years. Total age range was 11-50 years. Least number of patients was seen in more than 50 years age group. Mean age was 25.8+8.1 in Group-A and 25.8+7.8 in Group-B. This study showed that the incidence among males was slightly higher than females in both the groups. 52% of the pt was male in group A and 56% in Group B.

Table 2: Etiology/predisposing factors of keloids

Etiology		Group-A	Group-B	Percent
Predisposing factors	Acne	2	3	10
	Burn	2	1	6
	Ear Piercing	0	1	2
	Infection	5	6	22
	Trauma/surgery	11	10	42
Spontaneous		5	4	18
Total		25	25	100

Predisposing factor was found in 41(82%) patients in which trauma was commonest seen in 21(42%) patients, followed by infection. Other causes were acne, burn, ear piercing and in 9 (18%) patients spontaneous onset was seen.

Table 3: Site of keloids

Site	Group-A	Group-B	Frequency	Percentage
Chest	15	14	29	58
Back	1	1	2	4
Ear Lobe	0	1	1	2
Shoulder & upper extremity	7	7	14	28
Leg	2	2	4	8
Total	25	25	50	100

In this study it was observed that majority of keloids were seen over chest in 29(58%), followed by upper extremity 9(18%), shoulder, leg, back and earlobe.

Table 4: Clinical response in relation to duration of keloid

Duration of Keloid	<5 yr n (%)	>5 yr n (%)	ITT	Per protocol
Response			P value	
PR	0 (0)	2 (10)	<0.05	<0.05
FR	1 (3.3%)	4 (20)		
GR	4 (14)	3 (15)		
ER	24 (80)	9 (45)		
LOST	1 (3.3)	2 (10)		

Patients with <5 years of duration of lesion showed excellent response in 24(80%), good response in 4(14%) and 1(3.3%) showed fair response. The difference in overall response depending on duration of lesion was found to be significant (p<0.05).

Table 5: Improvement in signs and symptoms

Pruritus (n=37)	Group-A (N=19) n (%)	Group-B (N=18) N (%)	ITT	Per protocol
			P value	
Relieved	17 (89.4)	14 (77.7)	0.226	0.265
Not relieved	1 (5.3)	2 (11.1)		
Lost to follow up	1 (5.3)	2 (11.1)		
Cosmetic	(N=17) n(%)	(N=16) n(%)		
Relieved	12 (70.5)	9 (57)	0.299	0.057
Not relieved	4 (23.6)	7 (43)		
Lost to follow up	1 (5.9)	0 (0)		
Pain	(N=9) n(%)	(N=7) n(%)		
Relieved	8 (88.9)	6 (85.7)	0.964	0.832
Not relieved	1 (11.1)	0 (0)		
Lost to follow up	0 (0)	1 (14.3)		

In group-A, improvement in pruritus was seen in 89% of patients and 77.7% in Group-B. Pain was improved in 88% of patients in Group-A and 85% in Group-B. Similarly cosmetic appearance was improved in 70% of patients in Group-A and 57% in Group-B.

Table 6: Clinical response & comparison between group-A and group-B after 4th dose

At 4th Dose	Group-A n (%)	Group-B n (%)	ITT	Per Protocol Analysis
			P Value	
PR	1 (4)	1 (4)	0.639	0.818
FR	2 (8)	3 (12)		
GR	3 (12)	4(16)		
ER	18 (72)	15(60)		
Lost To Follow Up	1 (4)	2 (8)		

Out of 50 patients excellent response was seen in 18(72%) in Group-A and 15(60%) in Group-B respectively. Good response was seen in 3(12%) patient of Group-A and 4(16%) of patients in Group-B. Fair response was seen in 2 (8%) of patients in Group-A & 3(12%) patients in Group-B. Poor response was seen in 1 (4%) patients of group-A and 1(4%) patients of group-B. P value was found to be non-significant. (p>0.05)

Table 7: Early complication

Early complication	Bleomycin n(%)	Cryotherapy n(%)	ITT	Per protocol
			P value	
Pain	21 (84)	7 (28)	0.001	0.001
Ulceration	5 (20)	14 (56)	0.017	0.005
Erythema	6 (24)	13 (52)	0.074	0.028
Bulla formation	0	18(72%)	0.001	0.001

Pain was most common earliest complication in group A. It was seen in 21(84%) patients of group-A; whereas bulla formation was seen with 18 patients of Group-B. Similarly ulceration was seen in 5(20%) patients of group-

A & 14(56%) patients of Group-B. Erythema was seen in 6(24%) & 13(52%) patients of Group-A and Group-B respectively. Secondary Infection was seen in 2(8%) patients of Group-A.

Table 8: Delayed complications

Late complication	Bleomycin n(%)	Cryotherapy n(%)	ITT	Per protocol
			P value	
Hypopigmentation	8 (32)	10 (40)	0.827	0.871
Hyperpigmentation	5 (20)	3(12)	0.835	0.940
Atrophy	6 (24)	5 (20)	0.819	0.831
Telangiectasia	8 (32)	4(16)	0.444	0.260

Hypopigmentation was seen in 10 (40%) patients of Group-B and 8 (32%) of patients of group-A. Atrophy and Telangiectasia were more common in Group-A i.e. 6 (24%) and 8 (32%) respectively. Hyperpigmentation was seen in 5(20%) patients of Group-A and 3(12%) patients of group-B.

Discussion:

In this study 40% of patients in group-A and 44% of patients in group- B belonged to the age group of 16-25, followed by 32% of Group-A and 40% of Group-B in 26-35 age group. Mean age was 25.8+8.1 in Group-A and 25.8+7.8 in Group-B. The age range was 13 -50 years. More than 70 % of patients were within age of 30 years. In the study of Naeini et al [24] 66% of cases were between 15-30 years of age. In the study of Brian et al [2] and Murray the onset of keloids was seen most commonly between 10 and 30 years of age and uncommon at age of extremes. Out of 50 patients, 52% were males in group-A and 56% in group-B. Similarly 48% were female patients in group-A and 44% in group-B. Nishi et al [21] in their study found 53.5% of the subjects were male and 46.5% were female. Ketchum et al [6] found almost equal incidence among both males and females. In 56% of patients the duration of lesion was ≤5 years and >5years in 44% of patients. Mean duration was 4.48+2.4 in Group-A & 5.08+2.4 in Group-B. Gupta et al [12] in their study found mean duration to be 4.7 years. Cosman et al [20] in their study observed that most of the keloids occurred within 1 year of local trauma and others as early as to 2-4 weeks. In this study the longer duration of the lesions can be attributed to the negligence on the part of patients. The difference in distribution of duration of lesions among two groups was non-significant ($p>0.05$). Only 10% patients of 50 had positive family history. In Brian et al2 in their study reported familial incidence of 4.5% -16% in black and Hispanic population. Nishi et al [21] in their study reported 95% patients had no family history. In this study predisposing factor was found in 82% patients. In which trauma was the commonest cause seen in 42% patients, followed by infection in 22%, Other causes were acne, burn, ear piercing. Spontaneous onset of keloids was seen in 18% patients. Manoharan et al [22] in their study found trauma as predisposing factor in 50% cases, followed by acne in 15% cases, 10% patients developed keloid spontaneously. Other factors were infection, burn etc. Factors such as trauma, tension and hormones have been associated with keloid formation. In our study, 74% patients had complaint of pruritus, 66% patients had cosmetic disfigurement and pain was noted in 32% patients, 4% patient presented with restriction of movements. In Brian et al[2] study presenting signs and symptoms were pruritus, pain, cosmetic disfigurement, skin discoloration and restriction of movements. Nishi et al[21] in their study reported 70.6% sought medical intervention for cosmetic reason. In rajsekhar et al[11] study itching was seen in 100%, pain in 70%. In this study it was observed that common site of keloids was chest in 58%, followed by upper extremity & shoulder 28%, other sites were leg, back and ear lobe. Manoharan et al[22] in their study found that majority of patients i.e 52% had keloids on chest, 20% had on shoulder. Other sites were earlobe, back and leg. In this study, the primary outcomes evaluated were the percentage of decrease in height of keloid, pliability and relief of symptoms as the parameters of efficacy. The two groups were comparable with respect to age, sex, site and duration of lesion, with statistically no significant difference ($p>0.05$). Out of 25 patients, excellent response was seen in 18 (72%) patients, 3(12%) patients showed good response, followed by fair response in 2 (8%) patients and 1 (4%) patients showed poor response. Huu et al[16] who reported that 70.8 percent of lesions showed an excellent response, 17.5 percent of lesions showed a good response, 8.3 percent of lesions showed a fair response, and 3.3 percent of lesions showed a poor response. Out of 25 patients in 15 (60%) excellent response was seen and 4(16%) patients showed good response and fair response in 3(12%) and poor response in 1(4%). Har-Shai et al [19] in their study reported that there was 51% improvement with a single session of cryotherapy. Gupta et al [12] reported in their study 58% patients showed excellent response to >5 session of monthly intralesional cryotherapy, 33% of patients showed good response 8% showed fair response. In group A excellent and good result was seen in 72% & 12% of patients respectively, as compared to group B where it was 60% & 16% respectively. Fair response was seen in 8% in group A where as in Group B fair

response was seen only 12% cases. Poor response was 4% in both the groups.

Though more no of patients showed excellent response in Group-A, yet p value was found to be non-significant (p>0.05). In a study By Naeini et al [24], they observed in larger lesions (>100mm2), the therapeutic response to bleomycin was significantly better than cryotherapy combined with intralesional triamcinolon injection (p=.03). But they have used surface cryotherapy. In Group A, improvement in pruritus was seen in 89.4% of patients, followed by pain improved in 88% and 70% patients had improvement in cosmetic appearance and skin discoloration. In Group B 78% improvement was seen in pruritus, 85% in pain, followed by 57% in cosmetic appearance. According to Sharma et al [14] study improvement in pruritus, pain was seen with all i.e 100%, cosmetic appearance improved in 65% of patients. Patients with ≤5years of duration of lesion showed excellent response in 24 (80%) patients, 14% showed good response, no patients showed poor response. The difference in overall response depending on duration of lesion was found to be significant (p<0.05).

Early/Immediate complication: 84% of patients experienced pain at site of injection. Erythema was also seen in 28% patients. 5(20%) had ulceration at the site of injection which healed with the use of topical antibiotics in 2-3 weeks in all cases. No systemic side effect was noted in any patients: Delayed complication (2-6 months): In 5(20%) of patient's hyperpigmentation was seen; hypopigmentation in 32% cases, 6 (24%) cases showed atrophy and 8(32%) showed telangiectasia. Neini et al [24] observed hyperpigmentation in 75% of cases. Probably it's because they had used bleomycin alone. Early/Immediate complication: Pain was seen at site of injection in 7 (28%) of patient, 56% of patients developed ulceration, 92% cases developed bulla and subsequent crusting, Erythema was seen with 52% of cases. 2 (8%) patients developed secondary infection which got resolved with antibiotics. Delayed complication (2-6 months): hypopigmentation was seen in 10 (40%) of patients, atrophy in 5 (20%), telangietasia in 4 (16%), hyperpigmentation in 12% was seen, secondary infection was seen with 8% of patients. All studies reported mild-to-moderate postoperative pain with local edema and superficial necrosis in the first weeks following treatment. Weshahy et al [15] in their study observed Hypopigmentation in 20% of their patients; Van leeuwen et al [25] reported 7.5% cases developed wound infection. In both group incidence of adverse effects was statistically non-significant (p>0.05), Except for pain which was more in group-A; whereas ulceration and bulla formation was more in Group-B and it was statistically significant as well.

Conclusion

Our study concludes that combination therapies should be the preferred modalities of treatment in keloids rather than monotherapies. Both the treatment options showed promising result. Tramcinolone plus Bleomycin was found to be slightly better in terms of efficacy as compared to crytherapy plus tramcinolone.

References

1. Addison T. On the keloid of Alibert and on true keloid. In Shelley WB, Crissey JT, Stokes JH (eds): Classics in Clinical Dermatology with Biographical Sketches. Springfield, Charles C Thomas, 1953; 93-94.
2. Brian Berman, Harlan Bieley C. "Keloids". J Am Acad Dermatol 1995; 33; 117-123.
3. Al-Attar A, Mess S, Thomassen JM, Kauffman CL, Davison SP. Keloid Pathogenesis and Treatment. Plast ReconstrSurg 2006; 117:286-300.
4. Savant S. Hypertrophic scars and keloids. In. Textbook of dermato surgery and cosmetology. 2 editions. ASCAD- Mumbai 2008; 316-330
5. Griffith BH. The treatment of keloids with triamcinolone acetonide. Plast Reconstr Surg 1966;38: 202-8.
6. Ketchum LD. Smith J, Robinson DW, Masters FW. The treatment of hypertrophic scar, keloid and scar contracture by triamcinolone acetonide. Plast Reconstr Surg 1966; 38:209-18.
7. Stucker FJ, Shaw GY. An approach to management of keloid. Arch Otolaryngol Head Neck Surg 1992; 118:63-7.
8. Alster TS, Tanzi EL. Hypertrophic scars and keloids etiology andmanagement. Am J ClinDermatol 2003;4:235-43
9. Espana A, Solano T, Quintanilla E. Bleomycin in the treatment of keloids and hypertrophic scars. DermatolSurg 2001; 27:23-7.
10. Bodokh I, Brun P. The treatment of keloids with intra lesional Bleomycin. Ann Dermato lVenereol 1996;123:791-4
11. Rajshekar, S.B., et al. "A clinical study in management of hypertrophic scars and keloids with intralesional injection of Bleomycin." JEMDS 2015:4:68:11902-11905
12. Gupta S, Kumar B. Intralesional cryosurgery using lumbar puncture and/orhypodermic needles for large, bulky, recalcitrant keloids. Int J Dermatol 2001; 40:349-53.
13. Malakar S, Malakar R. Intralesional cryosurgery: Consequences, cautions and precautions. Indian J Dermatol 2000;45:100-1
14. Saurabh Sharma, Kajal Vinay, Roopam Bassi Treatment of Small Keloids Using Intralesional 5-fluorouracil and Triamcinolone Acetonide versus Intralesional Bleomycin and

Triamcinolone Acetonide J Clin Aesthet Dermatol. 2021; 14(3):17– 21.
15. Weshahy AH, Abdel Hay R. Intralesional cryosurgery and intralesional steroid injection: a good combination therapy for treatment of keloids and hypertrophic scars. Dermatol Ther. 2012; 25:273–276.
16. Kabel AM, Sabry HH, Sorour NE,et al.Comparative study between intralesional injection of bleomycin and 5-f uorouracil in the treatment of keloids and hypertrophic scars. J Dermatol Dermatol Surg. 2016; 20(1):32–38.
17. Omo-Dave P: Genetic studies on keloids. J natl Med Assoc 1975; 67:428.
18. Crockett DJ. "Regional keloid susceptibility". Br J Plast Surg., 1964; 17: 245.
19. Har-Shai Y, Amar M, and Sabo E. Intralesionalcryotherapy for enhancing the involution of hypertrophic scars and keloids. Plast Reconstr Surg. 2003;111:1841
20. Cosman B, Crikelair GF, Ju MC, et al. keloids" Plast Reconstr Surg. 1961; The Surgical Treatment of Keloids. Plastic and Reconstructive Surgery, 27, 335-358.
21. Nishi N, Rajashekar TS. A comparative study of effectiveness of cryotherapy with intralesional triamcinilone vs fractional CO2 laser with topical betamethasone for the treatment of keloids. J Cutan Aesthet Surg 2022; 15:254-9.
22. Manoharan A et al. analysis of risk factor in keloid Int J Res Dermatol. 2020 Mar; 6(2):138-141.
23. Lahiri A, Tsiliboti D, Gaze NR: Experience with difficult keloids. Br J PlastSurg 2001, 54:633-5.
24. Naeini FF, Najafian J, Ahmadpour K. Bleomycin tattooing as a promising therapeutic modality in large keloids and hypertrophic scars. Dermatol Surg. 2006; 32:1023-1029.
25. Van Leeuwen MCE, van der Wal MBA, Bulstra AEJ, et al. Intralesional cryotherapy for treatment of keloid scars: a prospective study. Plast Reconstr Surg. 2015; 135:580–589.