

Original Research Article

A study of verapamil in treatment of keloid

Yogesh M. Shah*, Adit M. Garg, Gaurav Paliwal, Amir S. Ansari,
Chandni Jain, Rashmi Rastogi

Department of Dermatology, Venereology and Leprosy, Era's Lucknow Medical College and Hospital, Lucknow, Uttar Pradesh, India

Received: 22 December 2017

Accepted: 13 February 2018

***Correspondence:**

Dr. Yogesh M. Shah,

E-mail: dr.yogeshshah.21@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Keloid is a common presentation in clinical practice. Symptoms due to keloid are mild, but disfigurement and functional impairment can be severe. It is difficult to treat. Intralesional, injection triamcinolone acetonide, has limited efficacy, causes adverse effects such as local dermal atrophy, telangiectasia and hypopigmentation. Injection verapamil is reported to have similar efficacy, but lesser side effects, and is cheaper. Aim was to study efficacy and adverse effects of intralesional verapamil in treatment of keloid.

Methods: An open label study on 25 patients of keloid, either gender, age 11 to 55 years at a medical college hospital. Injection verapamil 2.5 mg/ml was administered intralesionally, at an interval of 3 weeks, for a total of 6 sittings, over a period of 18 weeks. Vancouver scar scale (VSS) was used to assess the improvement. The statistical analysis was done using SPSS version 21.0.

Results: Median duration of keloids was 8 months. The mean VSS score before treatment was 7.68 which reduced to 4.28 after treatment. Mean percentage change in VSS score was 46.21%, very highly significant ($p < 0.001$). Physician's assessment was 'very good' in 32.0% and 'excellent' in 8.0%. The complaint of post-procedure pain was present in almost all.

Conclusions: Intralesional injection verapamil, gives very good to excellent improvement in 40% of patients of keloid. Post injection pain persists for more than 24 hours. Drug does not cause local dermal atrophy or hypopigmentation.

Keywords: Keloids, Intralesional, Verapamil, Efficacy, Vancouver scar scale

INTRODUCTION

Keloid is an area of benign overgrowth of fibrous tissue that usually develops after healing of a skin injury, and extends beyond the original defect.¹ Keloids clinically manifest as raised, hyper-pigmented, erythematous nodules or plaques, with an irregular border, making them visible and distinct from the surrounding skin.² Patients with darker skin have a higher prevalence for keloid than lighter skin.³ It is the fifth most common skin disease in adult black patients, in the United Kingdom.⁴

Symptoms of itch and pain due to keloid are mild, but the disfigurement and functional impairment can be severe. It leads to aesthetic and physical complaints, causing psychogenic turmoil and severe depression in affected individuals.⁵⁻⁷ Intralesional triamcinolone acetonide (TAC) is considered to be the first line of treatment, however it is effective only against younger keloids, response rate varies from 50% to 100%, and a recurrence rate of 9% to 50% is reported.⁸ Local side effects due to TAC include dermal atrophy, telangiectasia and pain at the site of injection.

Verapamil, a calcium channel blocker, and an antiarrhythmic agent, has emerged as a useful treatment modality in treatment of keloids.⁹ It is reported to decrease IL-6 and vascular endothelial growth factor in the central keloid fibroblasts, reducing cell proliferation, increasing apoptosis and expression of decorin, thus inhibiting fibroblast proliferation and migration and reducing keloid.¹⁰ It is reported that VPL has lesser side effects as compared to TAC, is cheaper and could be a suitable alternative to TAC.¹¹ Aim was to study efficacy and adverse effects of intralesional verapamil in treatment of keloids, by assessing clinical improvement using Vancouver scar scale (VSS).

METHODS

The study was carried out on 25 patients in Dermatology OPD of a medical college and hospital, Uttar Pradesh, India, over a period of one year and six months, with due permission of Institutional Ethics Committee. Keloid patients of either gender, in the age group 11 to 55 years, were included in the study. Patients with immunocompromised status, local infection, pregnant or lactating mothers and those who had received any specific treatment for keloid within previous 6 months were excluded. Sample size was calculated on the basis of decrease in volume of keloid.¹²

Injection verapamil (VPL) 2.5 mg/ml was administered intralesionally at an interval of 3 weeks, for a total of 6 sittings, over a period of 18 weeks (4.5 months). Injection Verapamil needs no dilution as it is available in the required concentration of 2.5 mg/ml (vial: 5 mg/2 ml). The lesion was infiltrated with the drug solution, until complete and uniform blanching of the lesion was achieved, using a disposable insulin syringe, and 26 gauge needle. No sedation/analgesia was used prior to the injection.

The details of the subject were recorded in a predesigned “case record form” which included the Fitzpatrick skin type, duration, site, number and various other parameters of the keloid. Height, pliability, vascularity, pigmentation and size of the keloid were assessed on VSS. VSS was assessed before treatment with Injection VPL, and after completion of the treatment at 18 weeks.

VSS is a validated tool to document a change in appearance of the scar and is widely used in clinical practice and research.¹³⁻¹⁵ It was first described by Sullivan in 1990.¹⁶ Vascularity, pliability, pigmentation, and height of the scar are the parameters assessed to determine the score, in VSS. The score for pliability ranges from 0 to 5, height and vascularity from 0 to 3 and pigmentation from 0 to 2, to give a maximum score of 13. The decreasing mean value of the score indicates clinical improvement in the scar.

Scar height was measured with calipers, scar pliability subjectively assessed by palpation, scar vascularity was

rated on visual inspection, and the rate of refill after blanching the keloid. Blanching was achieved by a transparent plastic sheet with VSS score sheet pasted on it, as suggested by Baryza and Baryza.¹⁵ Scar pigmentation was assessed after blanching, and comparing the scar color with the surrounding skin.

The percentage reduction in VSS was graded according to the quartile score with ≤25% reduction in VSS, graded as poor, 26-50% reduction as good, 51-75% reduction very good and >75% as excellent response.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS), version 21.0. Wilcoxon signed rank was used to assess the outcome. A ‘p’ value less than 0.05, indicated a statistically significant change.

RESULTS

A total of 25 patients of keloid, were treated with intralesional injection verapamil 2.5 mg/ml. All 25 patients completed the study. Male patients were 14 (56%) and female 11 (44%). Age of the patients varied from 12 years to 49 years, mean age was 30.72 (±11.23) years (Table 1). Family history of Keloid was present in 3 (12.0%) patients. The majority (64.0%) had Fitzpatrick skin type IV. Duration of Keloids ranged from 1 to 36 months with a median duration of 8 months (Table 1). The majority (92%) had one or two keloids; none of the patient had more than three keloids (Table 2). The majority (92%) of keloids were either on the chest or shoulders (Table 3).

Table 1: Demographic data.

| Demographic characteristics | | |
|------------------------------|---|----------------------|
| Gender | Male 14 (56%), Female 11 (44%) Ratio M:F- 1.27:1 | |
| Age in years | 12-49 | Mean 30.72±11.23 yrs |
| Family history | +ve 3 (12.0%) | -ve 22 (88%) |
| Fitzpatrick skin type | Type IV (64.0%) | Type V skin (36.0%) |
| Duration | 1 to 36 months | Median- 8 months |

Table 2: Number of keloids.

| Patients | Number of Keloids |
|-----------------|-------------------|
| 15 (60%) | One |
| 8 (32%) | Two |
| 2 (8%) | Three |

An assessment of VSS score was done at baseline and at 3 weeks, after the last injection, i.e. at 18 weeks from the first injection. At baseline, mean VSS score was 7.68±1.89 (median 8), which reduced to 4.28±2.21

(median 5) at final follow up, showing a mean change of 3.40 ± 1.44 (46.21%). On evaluating the data statistically, it was found to be significant ($p < 0.001$) (Table 4). Physician rated outcome was 'very good' to 'excellent' in 10 (40%) and 'good' in 11 (44%) cases. There were 4 (16%) cases in which outcome was evaluated as poor (Table 5).

Table 3: Location of keloids.

| Location on the body | Number of keloids (%) |
|------------------------|-----------------------|
| Chest | 14 (56) |
| Shoulder and upper arm | 9 (36) |
| Face and ear | 4 (16) |
| Back | 3 (12) |
| Thigh and leg | 2 (8) |

Table 4: Vancouver scar scale (VSS) score.

| VSS score (n=25) | Median | Mean | SD |
|--|---------------------------|------|------|
| At baseline | 8.00 | 7.68 | 1.89 |
| At 4.5 months (final follow up) | 5.00 | 4.28 | 2.21 |
| Mean change \pm SD (% change) | 3.40 ± 1.44 (46.21%) | | |
| Significance of change (Wilcoxon signed rank test) | $z = 4.401$; $p < 0.001$ | | |

Table 5: Physician rated outcome.

| Assessment | N=25 (%) |
|------------|----------|
| Poor | 4 (16) |
| Good | 11 (44) |
| Very good | 8 (32) |
| Excellent | 2 (8) |

Table 6: Side effects.

| Adverse effects | N=25 (%) |
|------------------|----------|
| Pain | 24 (96) |
| Hypopigmentation | 0 (0) |
| Telangiectasia | 0 (0) |
| Dermal atrophy | 0 (0) |

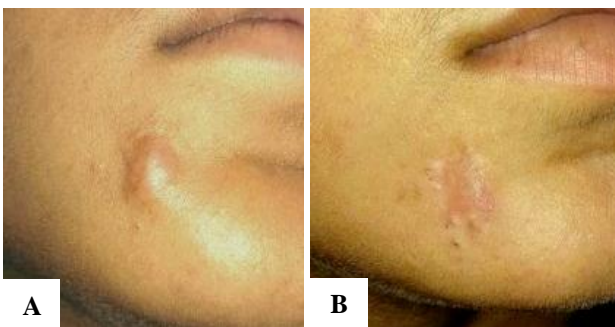


Figure 1: A= Before treatment; B= After 18 weeks of treatment (excellent improvement).

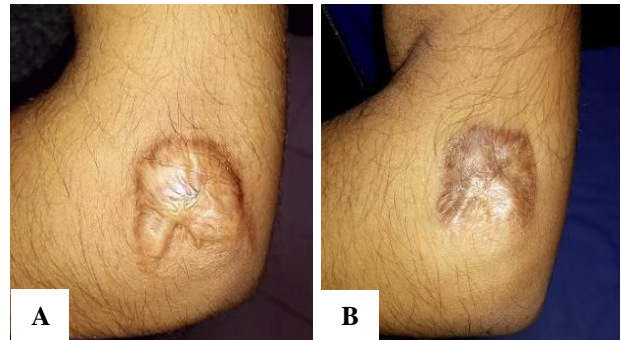


Figure 2: A= Before treatment; B= After 18 weeks of treatment (poor response).

Pain was the most common side effect as reported by 24 (96%) patients. None of the patients showed hypopigmentation, telangiectasia or atrophy (Table 6).

DISCUSSION

Keloids cause cosmetic disfigurement, functional impairment and a significant morbidity.^{6,7} A variety of treatment such as pressure therapy, silicone gel sheeting, intralesional bleomycin or interferon or corticosteroid injections, cryotherapy, surgical manipulation, laser and radiotherapy are being used. No particular treatment is suitable or effective in all the cases of keloid.¹⁷ Intralesional corticosteroids seem to be more effective, however they cause local adverse effects such as hypopigmentation, dermal atrophy and menstrual irregularities.

Among the emerging therapies, verapamil (VPL) is reported to be effective, relatively safer and much cheaper than TAC.⁹ Verapamil inhibits the synthesis and secretion of extracellular matrix molecules, including collagen, glycosaminoglycans, fibronectin and increases collagenase by inducing procollagenase expression.¹⁸ This study was done to evaluate efficacy of VPL in treatment of the keloid, in skin phototype IV and V. The drug VPL was used in the concentration of 2.5 mg/ml intralesionally, and VSS was used for assessment of the improvement.¹⁹⁻²¹

The actual amount of dose of the drug being injected, with respect to area and thickness of the keloid, cannot be measured as thickness of the keloid varies from lesion to lesion, and also within the lesion. Consequently in this study, complete blanching of the keloid at the time of intralesional injection, was considered to be the end point of the dose.

Majority of patients in this study, were in the age group ≤ 30 years; males being slightly more than females. Kant et al, Uzair et al, and Ahuja et al also observed predominance of keloid in the younger age group.^{11,20,22} The presentation of the patient in the younger is more probably due to a greater esthetic concern in the young. The duration of keloids, in the majority of subjects was

less than 12 months. Keloids were observed to be commonest on the chest (60%), followed by shoulder (20%), arm (18%) and face (10%), similar to the findings of Jannati et al.²³

In the present study, a mean reduction of 46.21% in all the parameters of the VSS, was observed at the end of 18 weeks. Uzair et al observed 36.75% reduction in VSS score, which was less than the improvement in the present study, however he had used only 3 injections of verapamil, one each at monthly interval.²⁰ In the present study, a total of 6 injections of VPL were administered, one each at 3 weeks interval, over a period of 18 weeks. Shanthi et al observed reduction in mean height of keloid from 4.33 mm to 0.15 mm, indicating an almost complete flattening, and maintenance of the improvement at 52 weeks.¹⁹ Results obtained by Shanthi et al are markedly higher than the present study, but she used a total of 8 injections of VPL over a period of 6 months.

Danielsen et al compared efficacy of intralesional verapamil and triamcinolone acetonide (TAC) after surgical excision, to prevent recurrence of the keloid. They observed a recurrence of 20% in the verapamil group but none in TAC group.²¹

The commonest adverse effect was persistent pain at the injection site. The pain persisted for 24 to 48 hours and some required analgesics for relief. Hypopigmentation, dermal atrophy, profuse sweating and menstrual irregularities, which are common adverse effects due to administration of corticosteroids, were absent following intralesional VPL.²³⁻²⁵

Limitations of the study

Therapeutic effect of injection verapamil was observed over a period of only 18 weeks (4.5 months); ideal period of observation could be about 1 to 2 years.

CONCLUSION

Intralesional verapamil gives very good to excellent improvement in a large number of patients. The drug is available as a thin solution, and is easy to inject, using a fine gauge needle. It does not cause adverse effects such as local dermal atrophy or hypopigmentation, and is relatively safe. Pain following verapamil is severe and analgesics may be required.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. 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.
2. Lemonas P, Ahmad I, Falvey DH, Jimenez G, Myers S. Keloid scars: the hidden burden of disease. J Pigmentary Disorders. 2015; 2:: 231.
3. Le Flore IC. Misconceptions regarding elective plastic surgery in the black patient. J Natl Med Assoc. 1980;72:947-8.
4. Child FJ, Fuller LC, Higgins EM, Du Vivier AW. A study of the spectrum of skin disease occurring in a black population in south-east London. Br J Dermatol. 1999;141:512-7.
5. Lee S-S, Yosipovitch G, Chan Y-H, Goh C-L. Pruritus, pain, and small nerve fibre function in keloids: a controlled study. J Am Acad Dermatol 2004;51:1002-6.
6. Bock O, Schmid-Ott G, Malewski P, Mrowietz U. Quality of life of patients with keloid and hypertrophic scarring. Arch Dermatol Res 2006;297:433-8.
7. Brown BC, McKenna SP, Siddhi K, McGrouther DA, Bayat A. The hidden cost of skin scars: quality of life after skin scarring. J Plast Reconstr Aesthet Surg. 2008;61:1049-58.
8. Cruz NI, Korchin L. Inhibition of human keloid fibroblast growth by isotretinoin and triamcinolone acetonide in vitro. Ann Plast Surg. 1994;33:401-5.
9. D'Andrea F, Brongo S, Ferraro G, Baroni A. Prevention and treatment of keloids with intralesional verapamil. Dermatology. 2002;204:60-2.
10. Giugliano G, Pasquali D, Notaro A, Brongo S, Nicoletti G, D'Andrea F, et al. Verapamil inhibits interleukin-6 and vascular endothelial growth factor production in primary cultures of keloid fibroblasts. Br J Plast Surg. 2003;56:804-9.
11. Ahuja RB, Chatterjee P. Comparative efficacy of intralesional verapamil hydrochloride and triamcinolone acetonide in hypertrophic scars and keloids. Burns. 2014;40(4):583-8.
12. Lee JH, Kim SE, Lee AY. Effects of interferon-alpha2b on keloid treatment with triamcinolone acetonide intralesional injection. Int J Dermatol. 2008;47(2):183-6.
13. Nedelec B, Shankowsky HA, Tredget EE. Rating the resolving hypertrophic scar: comparison of the Vancouver Scar Scale and scar volume. J Burn Care Rehabil. 2000;21:205-12.
14. Li-Tsang CWP, Lau JCM, Liu SKY. Validation of an objective scar pigmentation measurement by using a spectrophotometer. Burns. 2003;29:779-84.
15. Baryza MJ, Baryza GA. The Vancouver Scar Scale: an administration tool and its interrater reliability. J Burn Care Rehabil. 1995;16:535-8.
16. Sullivan T, Smith J, Kermode J, Mclver E, Courtemanche DJ. Rating the Burn Scar. J Burn Care Rehabil. 1990;11:256-60.
17. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG. Hypertrophic Scarring and Keloids: Pathomechanisms and Current and Emerging

- Treatment Strategies. *Molecular Med*. 2011;17(1-2):113-25.
18. Copcu E, Sivrioglu N, Oztan Y. Combination of surgery and intralesional verapamil injection in the treatment of the keloid. *J Burn Care Rehabil*. 2004;25:1-7.
 19. Shanthi FM, Ernest K, Dhanraj P. Comparison of intralesional verapamil with intralesional triamcinolone in the treatment of hypertrophic scars and keloids. *Indian J Dermatol Venereol Leprol*. 2008;74(4):343-8.
 20. Uzair M, Butt G, Khurshid K, Suhail PS. Comparison of intralesional triamcinolone and intralesional verapamil in the treatment of keloids. *Dermatol Online*. 2015;6(3):280-4.
 21. Danielsen PL, Rea SM, Wood FM, Fear MW, Viola HM, Hool LC, et al. Verapamil is Less Effective than Triamcinolone for Prevention of Keloid Scar Recurrence After Excision in a Randomized Controlled Trial. *Acta Derm Venereol*. 2016;96:774-8.
 22. Kant SB, Van den Kerckhove E, Colla C, Tuinder S, Van der Hulst RRWJ, de Grzymala AAP. A new treatment of hypertrophic and keloid scars with combined triamcinolone and verapamil: a retrospective study. *Eur J Plast Surg*. 2018;41(1):69-80.
 23. Jannati P, Aref S, Jannati AA, Jannati F, Moravvej H. Comparison of Therapeutic Response of Keloids to Cryotherapy Plus Intralesional Triamcinolone Acetonide or Verapamil Hydrochloride. *J Skin Stem Cell*. 2015;2(1):7-12.
 24. Manuskiatti W, Fitzpatrick RE. Treatment response of keloids and hypertrophic sternotomy scars. *Arch Dermatol*. 2002;138:1149-55.
 25. Bilal M, Tahmeedullah, Irfanullah, Shah SA. Clinical outcome of intralesional corticosteroid versus intralesional Verapamil in the treatment of post burn Keloid scars of the head and neck region. *Pak J Surg*. 2013;29(4):263-8.

Cite this article as: Shah YM, Garg AM, Paliwal G, Ansari AS, Jain C, Rastogi R. A study of verapamil in treatment of keloid. *Int J Res Dermatol* 2018;4:176-80.