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Comparative efficacy of intralesional verapamil hydrochloride and triamcinolone acetonide in hypertrophic scars and keloids☆

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ABSTRACT

There is not much level 1 evidence based literature to guide management of hypertrophic scars and keloids despite an array of therapeutic modalities at disposal. Intralesional (i/l) triamcinolone injections have remained a gold standard in non surgical management. Sporadic reports on use of i/l verapamil suggest its efficacy. Since verapamil has not found sufficient mention as an effective alternative modality, it was decided to undertake a randomized study which could also address some additional clinical parameters.

A randomized, parallel group and observer blinded comparison with 40 patients (48 scars) was carried out to compare the effects of i/l triamcinolone (T) (22 scars) and verapamil injections (V) (26 scars). 1.5 ml was the maximum indicative volume decided in the study protocol for both the drugs (triamcinolone @40 mg/ml and verapamil @ 2.5 mg/ml). Patients included were aged between 15–60 years with scars ranging between 0.5–5 cm (but total area roughly $<6\ cm^2$), and scars under 2 years duration. Patients with keloidal diathesis were excluded. Injections were scheduled every three weeks until complete flattening of the scar or eight sessions, which ever came earlier. No concomitant therapies like massage, silicone gel or pressure garments were used. Scar evaluation at each stage was done by serial photographic records as well as by Vancouver Scar Scale (VSS). Comparative survival analysis between the two drugs was done using Kaplan Meier curves, and VSS scores were analyzed using Wilcoxon test and log rank test.

Mean zero VSS scores were achieved with treatments in respect of scar height (T-12 weeks, V-21 weeks), vascularity (T-15 weeks, V-18 weeks) and pliability (T-15 weeks, V-21 weeks). The improvement in scar vascularity and pliability kept pace with decrease in scar height, in both the groups. There was not much difference in the rate of change of scar pigmentation with either drug but almost 60% patients in both the groups regained normal pigmentation.

Our study adds to evidence of verapamil's capability in flattening the raised scars. With an extremely low cost and fewer adverse effects it deserves better positioning in the wide armamentarium against hypertrophic scars. It also offers several therapeutic possibilities to alternate with triamcinolone or be used simultaneously in larger (or multiple) scars.

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1. Introduction

Keloids and hypertrophic scars are dermal fibro-proliferative disorders unique to humans [1], which may lead to disfigurement, pain and pruritus [2]. Their management is still challenging as there is no universally accepted treatment regimen [3] and not much level 1 evidence based literature to guide management. This is despite an array of therapeutic modalities at disposal, because there are a multitude of etiological factors [4], less well understood pathophysiology [5], wide spectrum of disease [6] and limitations of targeted therapies. For less extensive hypertrophic scarring and keloids, intralesional (i/l) triamcinolone injections have remained a gold standard in non surgical management. It has been reported that scars treated with triamcinolone acetonide (T) showed decreased levels of the proteinase inhibitors alpha$_2$-macroglobulin and alpha$_2$-antitrypsin in the scar [5]. This leads to decreased collagenase (matrix metalloproteinase 1/MMP1) degradation which controls excessive and abnormal collagen seen in hypertrophic scars and keloids [5].

In 1990, Lee and Ping demonstrated that calcium channel blockers such as verapamil lead to decreased extracellular matrix production in scars [7]. It was further demonstrated that verapamil depolymerizes actin filaments to modify fibroblast morphology with a consequent increased secretion of procollagenase [8,9]. Subsequently, there have been sporadic reports of its use in hypertrophic scars and keloids suggesting its efficacy [10–12], but these studies were uncontrolled and with limited number of subjects. Moreover in two of these reports, i/l verapamil injections were used following excision of the lesion, and in combination with compression [10] or silastic sheets [11] for prophylaxis. The first randomized controlled trial to study verapamil was conducted by Margaret et al. [13] which suggested that i/l verapamil may be as effective as triamcinolone in the treatment of hypertrophic scars and keloids. Since this report was the only confirmatory evidence available in literature, and in spite of which verapamil has not found sufficient mention as an effective alternative modality in the treatment of hypertrophic scars and keloids, it was decided to undertake another randomized study which could also address some additional clinical parameters.

2. Patients and methods

The study was conducted in the Department of Burns and Plastic Surgery, Lok Nayak Hospital and Associated Maulana Azad Medical College, New Delhi. Approval of institutional ethics committee was obtained before commencing the study. Subjects were recruited between July 2011 and August 2012 from the outpatient clinic. It was a randomized, parallel group and observer blinded comparison between i/l triamcinolone (T) and verapamil injection (V). 1.5 ml was the maximum permissible injected volume of triamcinolone (concentration 40 mg/ml) and verapamil hydrochloride (concentration 2.5 mg/ml). Inclusion criteria included patients aged between 15–60 years old, scars of 0.5–5 cm in maximum dimension, regardless of the shape, but total area roughly $<6\ cm^2$ and scars under 2 years duration. Patients with evidence of any infection or ulcer, in or near the scar, were excluded. Also excluded were pregnant females, and patients with a history of prior treatment with any intralesional injection. In patients with multiple hypertrophic scars two sites were recruited only if their total area appeared $<6\ cm^2$. No attempt was made to distinguish between hypertrophic scars and keloids but patients with keloidal diathesis were excluded on the basis of past personal or family history.

Detailed history and demographic parameters were recorded, including etiology, duration of scarring and prior treatments.

A minimum sample size of 44 scars (22 in each group) was calculated for a non inferiority trial design with triamcinolone as standard treatment and verapamil as the experimental drug based upon an alpha error of 5% and power of 80%, assuming a non-inferiority limit of 30%, and at least 80% cure rate for each group. The patients were randomly allocated to two groups A and B using a computer generated random sequence. Scars in group A received i/l triamcinolone acetonide and scars in group B received i/l verapamil hydrochloride, every three weeks for a maximum of eight sessions or till complete flattening of the scar, whichever came earlier. The injections were made at several points in the lesion with an insulin syringe and 24 gauge needle to achieve complete and evenly distributed blanching of the lesion at endpoint. No sedation/analgesia was used at the time of injection. Scar flattening was defined as <1 mm scar height over 90% of the lesion, by visual assessment. No concomitant therapies like massage, silicone gel or pressure garments were used.

Scar evaluation at each stage was done by serial photographic records as well as by Vancouver Scar Scale (VSS) [14]. Scar height was accurately measured with calipers. Scar pliability was subjectively assessed by palpation. Scar vascularity was rated on visual inspection and the rate of refill after blanching. 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. Assessments were done by two independent observers (trainee registrars working in another unit of the department) who were blinded to the treatment groups. The mean value of their scoring was recorded. The decreasing value of the score indicates clinical improvement of the scar. All patients were followed until 24 weeks even if scar flattening was achieved before it.

The VSS scores, expressed as mean of all scars, were compared between Groups A and B using an unpaired 2 tailed *t*-test assuming a heteroscedastic sample variation at the various time point analyses. Comparative survival analysis between the two drugs was done using Kaplan Meier curves, and scores were statistically analyzed using Wilcoxon test and log rank test. Rate at which all the study parameters reduced to zero (zero is considered as the event), with the two drugs was compared for each of the four components of VSS. A p-value of <0.05 was considered to be statistically significant.

3. Results

A total of 40 patients (20 in each group) were recruited and followed up for the study duration. Forty-eight scars were