Abstract

Objective: To investigate the clinical effectiveness of silver nitrate (95%) for the treatment of verruca pedis comparing professional and self-application treatments.

Methods: A single-centre, two-armed randomized evaluation was conducted at a University podiatry clinic. A total of 113 participants (101 analysed) with ver- ruca pedis were included. Participants were randomized to either a clinical group, where silver nitrate was applied by a healthcare professional or a home group, where silver nitrate was self-applied. The main outcome measure was post-treatment pain, controlling for pre-treatment pain, and resolution of the verruca. Secondary outcome measures were participant satisfaction, partial reduction in the verruca and ease of use of the product.

Key findings: The study showed no significant difference between home treat- ment and clinically applied treatment for the treatment of verruca pedis in either primary outcome; however, a substantive difference in resolution between groups was recorded, with 34.0% full resolution and 26.4% partial res- olution in the clinical treatment group, and 18.8% full resolution and 37.5% partial resolution in the home treatment group. Participants widely reported general ease of use of the product. All participants reported a reduction in pain as a result of the intervention.

Conclusion: Silver nitrate has been shown to be a safe and effective treatment for verruca pedis, with equal success rates when compared between home and clinical applications.

Key Words

Verruca pedis, randomized evaluation, silver nitrate, warts

Introduction

In the UK, incidence of viral warts and verrucae in children and adolescents is estimated at between 3.9% and 4.9%, with both genders being equally predisposed to HPV infection (Leiding, 2012). The National Morbidity Survey data (1991-1992) suggests that almost two million people in England and Wales will see their General Practitioner for the treatment of cutaneous warts each year, at a cost of an estimated £40 million per annum (Thomas et al, 2006).

The cause of these cutaneous neoplasms is by the infection of the epidermal or mucosal cells with the Human Papilloma Virus (HPV) (Lynch et al, 2014). Entry of the virus in to the epidermal tissue is allowed via a breach in the epidermal surface, often resulting from earlier microtrauma or maceration. The virus infects the basal layer of the epithelium, causing hyperkeratinisation and eventually a visible focal proliferation at the stratum corneum (Khondker et al, 2012). The lesion can develop either singularly as a firm papule of hyperkeratotic tissue, or merge to form a cluster of lesions with a rough, scaly surface, which are referred to as 'mosaic'. Thickening of the stratum corneum can cause dermatoglyphics which are interruptions in the stratum corneum which form the lesion(s) (Lipsker, 2013).

Discomfort caused by raised epithelial proliferations over weight-bearing areas, a negative social perception and the duration of recalcitrant lesions are common initiators for clinical treatment (Lynch et al, 2014). Several observational studies have demonstrated that most viral warts and verrucae will regress naturally without treatment intervention (Williams et al, 1993) and this advice has been accepted as a valid management option (Sterling et al, 2014). However, the rate and success of resolution is variable and is likely to be dependent upon several factors, including host immunity status, age, HPV serotype, and site of infection

(Leiding, 2012). Spontaneous resolution of a wart or verruca can occur at any time from a few months to a few years in immune-competent adults (Sterling et al 2014).

From a clinical perspective, treatment is usually considered when lesions become symptomatic in terms of associated pain, enlargement or proliferation, haemorrhaging and causing distress (Lynch et al, 2014). Outside of these recommendations for treatment intervention, an expectant approach to management is often advised to patients, who are directed towards self-treatment with over-the-counter topical medicaments (Sterling et al, 2014).

Silver nitrate remains a common treatment for verrucae, especially for those patients at an increased risk of tissue breakdown and reduced healing capacity, due to the treatment's self-limiting superficial penetration into the epidermis (Kwok et al, 2012). Silver nitrate is an inorganic salt, classified as a caustic, anti-septic and astringent agent (Joint National Formulary Committee, 2015); therefore providing many uses in practice such as in the cauterization of wounds, removal of skin growths and granulation tissue (Monafo & Moyer, 1965; Vermeulen et al, 2007). In the management of verrucae, the clinical aim of treatment involves both the biochemical and physical destruction of the virus. The application simultaneously instigates localized tissue irritation, thereby initiating a host immune response to the virus (Medicines, 2011).

Two studies have evaluated silver nitrate against a black ink placebo for the treatment of verrucae and both reach similar findings (Yazar & Basaran, 1994; Ebrahimi et al, 2007). Yazar and Basaran reported a relatively high cure rate one month after the last application in the silver nitrate group (15/35, 43%) compared to 11% (4/35) in the placebo group. The more recent trial by Ebrahimi et al (n=60) evaluated 10% silver nitrate solution; finding a 23.3% cure rate, compared to 0% in the placebo after 3 weeks. There have been no

reported adverse side effects following the topical application of silver nitrate. Similarly few contraindications exist, except for those with hypersensitivity to silver nitrate or any other component in the formulation.

Strengths of 75% and 95% are frequently used in clinical practice; however, to date these have not been evaluated to determine their clinical effectiveness. In addition, self-administered application of silver nitrate is now commercially available, although awareness of its effectiveness in comparison to the clinical application by a health professional is unknown (Bray, 2007). The aim of this research was to evaluate the clinical effectiveness of using 95% concentration silver nitrate for the treatment of verrucae pedis, comparing professional and self-application treatments using application pencils. Secondary objectives included the collection of data relating to patient satisfaction with the treatment and the clinicians' experience and opinions of using this product.

Methods

Trial design

We randomized individuals in a single-centre, two-armed randomized evaluation comparing home and clinical application of 95% silver nitrate treatment for verruca pedis. The evaluation was given ethical approval via the University School Research Ethics Panel. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in approval by this panel.

Participants

Inclusion criteria was the diagnosis of one or more verruca. Exclusion criteria were: lack of mobility to use the self-treatment pencils; visual difficulties; dementia or incapacity to follow instructions. Participants were assessed against the inclusion criteria by a Health and Care

Professions Council (HCPC) registered podiatrist. Participants not suited for inclusion in the evaluation were given a choice of an alternative course of treatment.

Participants were recruited from advertisements placed in local GP surgeries, schools, health centres, podiatry private practices, around the campus of the University of Huddersfield and on social media sites. The advertisement invited participants to contact the University Of Huddersfield Podiatry clinic via email or telephone. The evaluation was carried out in the Podiatry Clinic at the University of Huddersfield, United Kingdom.

All participants were given an information sheet prior to consent being gained. All participants signed a consent form and were given a set of clinical notes which were documented, treated and stored within the university clinical facilities, to comply with data protection and assure patient confidentiality. Results from the evaluation were anonymised and kept on a password-protected computer, accessible only by the clinical evaluation personnel. A risk assessment was undertaken considering participant and clinical safety issues and appropriate risk management measures taken.

Outcomes and outcome measures

The primary outcome measures were post-treatment pain (as measured on a VAS at the final review of 20 weeks); and resolution of the verruca, categorized into “success” (full resolution of the verruca), “partial success” (up to 50% reduction in size) and “failure” (no change, or verruca enlarged or spread). The secondary outcome measures were participant satisfaction, partial reduction of the verruca and ease of use of the product. The secondary outcome measures were recorded by self-completed questionnaires which were given to all participants.

Interventions

Participants included for the evaluation were given a primary treatment of debridement of any overlying callus. Baseline data was obtained using a lesion chart and digital photograph

and the pain was recorded on a Visual Analogue Scale (VAS). The participant was then randomized to either home or clinically/professionally applied treatment.

Participants in the self-treatment arm of the evaluation were given silver nitrate pencils (95%) to take home and treat the verruca independently at weekly intervals for 10 weeks. The pack contained a silver nitrate pencil, a written instruction leaflet, a small abrasive file, and the clinical and emergency contact numbers in case of any localized skin irritation. The application method was described and demonstrated verbally, and a supplementary written patient advice sheet was given to all participants to ensure that they followed the same standardised instructions. Participants were asked to prepare the skin prior to each application by using the file to remove devitalised tissue at the lesion surface. At the end of the 10 week treatment period, participants were invited back the clinic by the researcher and assessed by an independent podiatrist, blinded to treatment arm, for an interim review, and at 20 weeks after the first application date for a final evaluation. At both reviews the verruca was digitally photographed, a lesion chart completed to record size dimensions and border shape, and a Visual Analogue Scale (VAS) for pain score completed by the participant.

The interval time for treatment application for both arms of the study was one week, as this was considered to be a more realistic application time based on clinical practice.

At these appointments, the verruca was digitally photographed, a lesion chart completed and a VAS completed by the participant. This process also reflects the routine clinical protocol for verruca management. If resolution had not been achieved, the lesion was debrided with a scalpel and silver nitrate was applied (95%). Further appointments were made as necessary with a maximum of 10 treatments. As for participants in the home treatment arm, for the purposes of obtaining outcome measurements for the trial, at the end of the 10 week treatment period participants were seen by an independent podiatrist. The

independent podiatrist was blind to treatment arm. This was completed as an interim review and was also done after 20 weeks after the first treatment for a final evaluation. At both of these reviews the verruca was digitally photographed, a lesion chart completed and a pain VAS completed by the participant. At both the interim or final review if verrucae were unresolved or a callous persisted, debridement was carried out

For participants in both intervention arms, the reduction or partial resolution of size of lesions was objectively measured by the use of a digital image with measurable parameters on the image and the use of a transparent lesion chart drawn over the lesion. Final judgement on complete resolution of all verrucae was assessed by an independent podiatrist who had not been involved in the study.

At the 20 week final review, all participants were given a questionnaire to complete, at this appointment, about their experiences. The findings of satisfaction and ease of use are reported here; other findings will be reported in subsequent publications.

Sample size

A sample size calculation determined that under a standard level of significance (0.05) a total of 102 participants (51 in each arm of the trial) would be sufficient to reject the null hypothesis of equivalence of the population means with 80% power; assuming a medium sized effect on the primary outcome of post-treatment pain levels. Hence this number was set as the target minimum sample size to be recruited.

Randomization

Patients were randomized to either home or clinical treatment using the sealed opaque envelope method. Simple randomization without blocking was utilized. Patients could not be blinded to treatment allocation.

Statistical analysis

The sample was summarized descriptively. Exploratory analyses were conducted to assess the distribution of the post-treatment VAS pain outcome and the requirement for an appropriate data transformation; to ensure that the frequencies of each of the categories of the treatment result were sufficient for analysis; and to ensure that appropriate assumptions were met for inferential procedures.

An analysis of covariance (ANCOVA) was conducted on the data, using post-treatment VAS pain as the outcome, controlling for pre-treatment pain. An ordinal logistic regression was also conducted on the data, using treatment result as the outcome, with "success" defined to be the reference category.

Missing resolution data was imputed under the conservative assumption of non-resolution. This analysis was considered to be an intention-to treat analysis and was conducted including all patients randomized to home treatment or clinical application. A parallel per-protocol analysis was also conducted on participants who were followed through to analysis. For the pain outcome, missing data was imputed using expectation maximization; with parallel ITT and PP analyses also conducted.

Results

Participant flow

Participant flow is summarized in Figure 1.

Descriptive and exploratory analysis

Data was collected from 113 participants recruited over the course of 12 months. There was no missing data on the post-VAS pain variable. Twelve cases (10.6%) had missing values on the treatment result variables, with respect to resolution. Little's test for missing data revealed that despite the disparity of missing outcomes in the home treatment and clinical treatment groups, there was no evidence that missing items were not missing at random.

Missing values were imputed as non-resolution. The analysis of this variable was conducted on the remaining 101 cases as a per-parallel per protocol analysis, leading to a study with 80% power to detect any positive benefit of one form of treatment over the other form of treatment.

The sample is summarized in Tables 1 and 2.

Analysis of data distributions and detrended Normal Q-Q plots indicated a certain degree of non-significant skew of the post-VAS pain variable. Reciprocal and logarithmic transformations did not eliminate the skew; and furthermore the large numbers of zero values in the original data set led to these values being disregarded in the transformed variables. Hence analysis was conducted on the untransformed variable.

No relationship was found to exist between the grouping and controlling variable in the ANCOVA (point-biserial correlation coefficient, r=0.120; p=0.205).

A test of parallelism found no evidence that the relationships between the grouping variable and the logits of the treatment result were not the same for all the logits ($\chi^2_{(1)}$=1.49; p=0.222); indicating that an ordinal logistic regression analysis on this variable would be appropriate.

Pain outcome

An ANCOVA conducted on the post-VAS pain outcome measure found no evidence for a significant difference in post-treatment pain levels amongst participants receiving home treatment and participants receiving clinical treatment ($F_{1,97}$=0.100, p=0.752 in the ITT analysis; $F_{1,110}$=0.032; p=0.859 in the PP analysis). The controlling variable, pre-treatment VAS pain score, was significantly associated with the outcome ($F_{1,97}$=41.8, p<0.001 in the ITT analysis; $F_{1,110}$=44.7, p<0.001 in the PP analysis). The adjusted R^2 value for this model (0.288 in the ITT analysis; 0.158 in the PP analysis) indicated that the model was a moderate-to-good fit to the data.

All participants who reported non-zero pain at baseline reported a substantive reduction in pain as a result of the treatment; with the ITT analysis revealing a mean pain reduction of 3.30 points on the VAS (SD 2.46); and the PP analysis revealing a mean pain reduction of 3.98 points on the VAS (SD 2.27)). Both analyses revealed similar levels of pain reduction in the home and clinical application groups which were not significantly different in the two groups. The ITT analysis revealed a reduction of 3.19 points on the VAS scale (SD 2.39) in the home treatment group, and a reduction of 3.39 points on the VAS scale (SD 2.55) in the clinical treatment group (p=0.717). The PP analysis revealed a reduction of 2.21 points on the VAS scale (SD 2.61) in the home treatment group, and a reduction of 2.77 points on the VAS scale (SD 2.68) in the clinical treatment group (p=0.293).

Resolution outcome

Complete resolution occurred in 27 (23.9%) of the 113 participants included in the intention-to-treat (ITT) analysis (26.7% of the 101 patients included in the per-protocol (PP) analysis). An ordinal regression conducted on the treatment result variable found that there was no evidence that a model with group as a predictor was a significantly better fit than a null model with no predictors (($\chi^2_{(1)}$=3.18, p=0.0.075 for the ITT analysis; $\chi^2_{(1)}$=1.22,p=0.269 for the PP analysis). However, a substantive difference in favour of clinic treatment was observed with respect to the treatment result outcome: participants randomised to the clinic group had a greater resolution success of 18 out of 55 participants (32.7%) compared to 9 out of 58 participants (15.5%) in the home treatment group in the ITT analysis; and 18 out of 53 participants (34.0%) compared to 9 out of 48 participants (18.8%) in the home treatment group in the PP analysis. Additionally, a further 18 participants (31.0%) in the home treatment group and 14 participants (25.5%) in the clinic group showed a 50% reduction in size of verrucae in the ITT analysis.

Secondary outcomes

44 out of 58 participants from the home treatment arm and 39 out of 55 participants from the clinic treatment arm completed the questionnaires. 19 out of 42 participants (45.3% of valid responses) found the treatment “easy” or “very easy” to apply. Only 6 patients (14.3%) found the treatment “difficult” or “impossible” to apply. Application instructions were correspondingly rated well, with all participants rating them as “OK” or better.

Overall, 30 out of 40 participants (75.0%) rated themselves satisfied with home treatment; 32 out of 38 participants rated themselves satisfied with clinic treatment. This difference in proportions was not clinically significant (p=0.788).

Discussion

The findings of this evaluation confirm that there is no evidence that whether a patient receives home or clinic treatment has any significant effect on post-treatment pain score, controlling for pre-treatment pain levels. Both arms of the evaluation indicate a positive benefit of the treatment, regardless of whether applied at clinical or at home, measured in terms of pain reduction, verruca resolution and patient satisfaction.

Despite the observed difference in outcomes (in terms of degree of resolution) between the treatment groups, the findings also confirm that there is no evidence that home treatment and clinical treatment are statistically different in effectiveness.

Strengths and limitations

This randomized evaluation was not registered as a clinical trial. RCTs may still be considered by many to be the strongest form of evidence for clinical decision making (Steen & Dager, 2013). Close matching of participants on demographic characteristics across both treatment arms following randomisation eliminates the influence of these variables on the assessment of the effectiveness of treatment regime. However, the lack of a control group

precludes definitive statements relating to the effectiveness of sliver nitrate *per se* in the current study, in which a total of 38 (34%) participants recruited had had a verruca for less than one year. It has been reported that 30% of warts resolve without treatment by 32 weeks (de Haen et al, 2006), and hence it could be argued that a proportion of these lesions included in the analysis would have shown spontaneous regression even without any intervention. Furthermore 33% of participants had had a verruca for 5 years and over, and had tried numerous other treatments such as acids without success. De Haen et al highlights that some verrucae may be particularly resistant to not only spontaneous resolution, but to any treatment. Both arguments suggest that it is possible that the success rate of silver nitrate could have been over- or underestimated due to the lack of comparison to a control. According to Gibbs and Harvey (2009), a 'wait and see' approach or placebo group has a success rate of around 30%. Bristow and Greenwood (2009) argue the proposed treatment must therefore be significantly greater than this figure to be considered effective.

Participants in both arms of this evaluation were assessed at week 20 (approximately 10 weeks after the last treatment), by podiatrist independent of and impartial to the evaluation, effectively blinded to the treatment arms. This assessment sought to gain an objective view of whether the verruca had resolved, partially resolved or remained the same. Kwok et al (2012), however, recommends a follow-up interval of 6 months to fully assess complete resolution or recurrence, given that the virus can have a latent configuration. Assessment at six months would not only have allowed for the fact that the human papilloma virus may remain dormant within epithelial cells without visible disease, but would also allow time for any response mediated by the immune system to be observed. Therefore it is possible that patients who showed a significant reduction in the size of lesions may have seen a complete resolution if treatment were continued after the 10 week cut-off for the evaluation period.

Keefe & Dick (1990) used a questionnaire to look at long-term outcomes and found that 83% of participants believed they were cured at the end of the treatment period, but only 57% were cleared of warts after a median follow-up time of 19 months.

The assumption that those patients for whom resolution data at outcome was missing had non-resolved verruca is thought to be conservative. The most likely reason for a patient failing to attend a follow-up appointment is that their verruca had been resolved to their satisfaction. Even so, the findings of the trial were not sensitive to this assumption, with both the ITT and PP analyses concluding lack of evidence for a difference in home and clinical application with respect to this outcome. Findings related to the pain data were also not sensitive to missing data items on this outcome.

Comparison of findings against other studies

The full resolution rate in the current study of 34.0% and 18.8% in the clinical and home treatment groups are broadly comparable with the findings of earlier studies of the efficacy of silver nitrate (Yazar and Basaran, 1994; Ebrahimi et al, 2007). Direct comparisons of resolution rates cannot be drawn between these two studies and this evaluation due to differences in the concentration of silver nitrate used; for instance Ebrahimi et al (2007) investigated a solution of 10%. A comparison of clearance results from other clinical-based treatments also indicates similar results to the findings of the current study: resolution rates of 33.7% were reported by Cockayne et al (2012); of 39% by Sjoerd et al (2010); of 9% by Gibson et al (1984); and of 47% and 44% by Ahmed et al (2001) in cryotherapy groups; and of 42% by Khattar et al. (2007) and 24% by Sjoerd et al (2010) in salicylic acid groups. These findings suggest that silver nitrate treatment can compete against other clinical interventions in the treatment of verrucae pedis. However clinical heterogeneity restricts the validity of direct comparisons between studies.

Implications for clinical practice

This randomized evaluation of the clinical effectiveness of silver nitrate (95%) for the treatment of verruca pedis revealed no evidence for a significant effect of treatment environment (home or clinic treatment) on either post-operative pain score or treatment result. Although the health economics data was not established, silver nitrate is a safe, cost-effective and easy to use treatment option for verruca. It is suitable for application for any patient profile, offering the clinician an alternative option for treatment. Future research could focus on comparing the resolution rates of silver nitrate against other commercially available treatment modalities.

Conflicts of Interest

There were no conflicts of interest.

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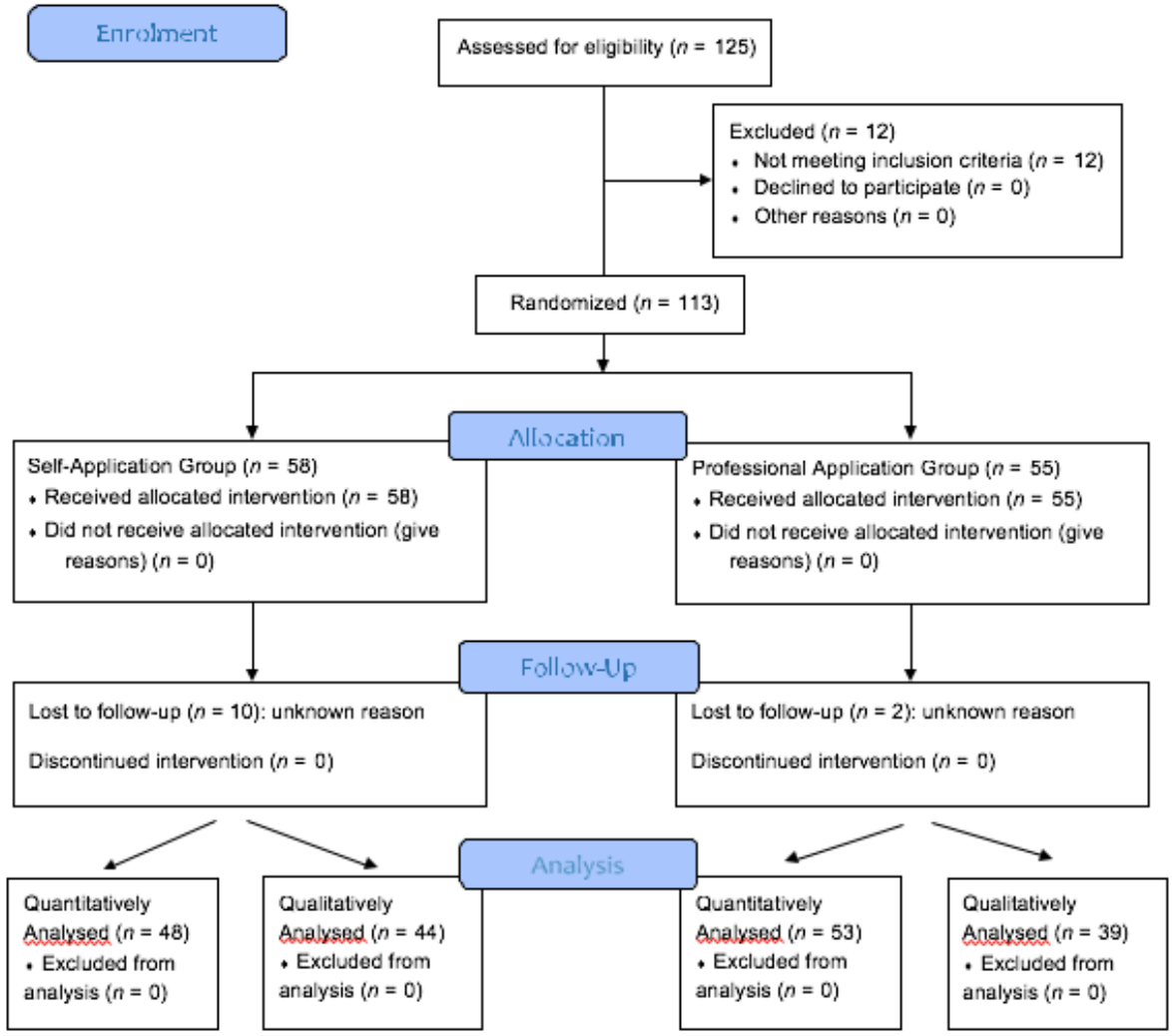
Figures

Figure 1: Participant Flow Diagram



Tables: ***Table 1: descriptive summary of sample***

Factor	Frequency (valid %)		
	Home treatment (N=58)	Clinic treatment (N=55)	All participants (N=113)
Gender			
Male	23 (39.7%)	21 (38.2%)	44 (38.9%)
Female	35 (60.3%)	34 (61.8%)	69 (61.1%)
Location			
Forefoot	37 (63.8%)	33 (60.0%)	70 (61.9%)
Forefoot, plus mid and/or rearfoot	13 (22.4%)	12 (21.8%)	25 (22.2%)
Rearfoot	8 (13.8%)	10 (18.2%)	18 (15.9%)
Duration			
Less than 1 year	25 (43.1%)	13 (24.1%)	38 (34.0%)
1-4 years	16 (27.6%)	21 (38.9%)	37 (33.0%)
5 years and over	17 (29.3%)	20 (37.0%)	37 (33.0%)

Table 2: Primary and Secondary Outcome Results	Home treatment	Clinic treatment	All participants
	Numerical Variable - Mean (SD)		
Age (years)	42.8 (22.8)	43.8 (21.6)	43.3 (22.1)
Result			
Success	9 (18.8%)	18 (34.0%)	27 (26.7%)
Partial success	18 (37.5%)	14 (26.4%)	32 (31.7%)
No change/enlargement	21 (43.8%)	21 (39.6%)	42 (41.6%)
Pre-treatment VAS pain score	3.24 (3.12)	3.98 (3.05)	3.61 (3.09)
Post-treatment VAS pain score at 10 or 20 week review	0.948 (1.81)	1.25 (2.07)	1.10 (1.94)
Change in VAS pain score	2.29 (2.58)	2.72 (2.66)	2.50 (2.62)