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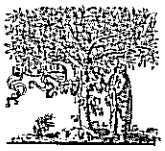

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SHORT COMMUNICATION

Efficacy of a homeopathic preparation in control of post-operative pain—A pilot clinical trial

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Summary
Background: Despite modern surgical technique and anaesthesia, post-operative pain following ambulatory surgery remains an important cause of delayed hospital discharge, readmission, and post-operative visits to primary care physician. Traumeel S® is a homeopathic complex preparation widely used in German speaking Europe for trauma and orthopaedic pain.
Methods: We performed an open, quasi-randomized triple-arm clinical trial to evaluate the efficacy of two regimens of Traumeel S® in minimizing post-operative pain and analgesic consumption following elective *Hallux valgus* surgery. A total of 30 patients were assigned to the single injection, the injection + oral intake (PO) or the control group. Repeated measures of maximal pain at rest during 13 days post-operative were evaluated using a linear mixed effects model. The total consumption of analgesics was also compared between the three groups.
Results: The single injection and injection + PO groups experienced lower pain scores as compared to the control group ($p = 0.02$ and 0.05, respectively). There was no significant difference between the single injection group and the injection + PO groups. Similarly, the mean total consumption of analgesics was lower in the single injection and the injection + PO groups than in the control group but the difference was not statistically significant.
Conclusion: In this pilot study, Traumeel S® demonstrated efficacy in minimizing post-operative pain following repair of *H. valgus*. These promising results should be validated in a randomized, double-blinded, placebo controlled trial.

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Table 1 Composition of the homeopathic-complex Traumeel S®

Component	Homeopathic dilution	Concentration
Arnica montana	D2	2.2×10^{-2} µl
Calendula officinalis	D2	2.2×10^{-2} µl
Atropa belladonna	D2	2.2×10^{-2} µl
Aconitum napellus	D2	1.32×10^{-2} µl
Bellis perennis	D2	1.1×10^{-2} µl
Hypericum perforatum	D2	6.6×10^{-3} µl
Echinacea angustifolia	D2	5.5×10^{-3} µl
E. purpurea	D2	5.5×10^{-3} µl
Symphytum officinale	D6	2.2×10^{-6} µl
Matricaria chamomilla	D3	2.2×10^{-3} µl
Achillea millefolium	D3	2.2×10^{-3} µl
Mercurius solubilis Hahnemanni	D6	1.1×10^{-6} ml

1. Introduction

The management of postoperative pain following ambulatory surgery has been found to be inadequate in a number of studies [1–5]. Pain is the most common reason for delayed discharge and unanticipated readmission following ambulatory surgery [6,7], and for contacting the family physician after discharge [8]. Nearly a third of patients have moderate to severe pain 24 h after ambulatory surgery [9] with eleven percent experiencing severe pain [10]. Moderate-to-severe pain can last for up to one week after surgery [9].

TRAUMEEL S® is an over-the-counter homeopathic complex preparation, sold widely in Germany, Austria and Switzerland for over 50 years. It is one of the most popular alternative medications in Germany, selling approximately four million ampoules annually [manufacturer information]. Traumeel S® has been found effective in trauma [11–14],[1] post-chemotherapy stomatitis [15] and in spinal syndrome [16], although these studies are generally of poor methodology. Laboratory evidence has accrued regarding its purported mechanism of action (e.g., [17,18]). Traumeel S® is composed of extracts from a combination of plants and minerals (see Table 1). Extensive safety data from a large survey of Traumeel S® showed adverse events in 0.0035% of 3.5 million cases (manufacturer information). These events were all mild, and ceased with discontinuation of treatment. No drug interactions have been reported.

To our knowledge, there has been no randomized controlled trial assessing the effectiveness of Traumeel S® for the relief of acute pain in patients following ambulatory surgery. Therefore, before implementing a randomized double blind controlled trial, we performed this preliminary study to assess pain and analgesic consumption after ambulatory surgery for *Hallux valgus* correction in patients receiving Traumeel S® as compared with control. The results from this analysis will be used to compute the sample size required for an adequately powered, subsequent large randomized double blind trial comparing Traumeel S® and placebo.

[1] Three of these four German language articles were published in non-peer-reviewed journals and are thus not indexed in Medline.

2. Materials and methods

We performed an open, prospective, triple-arm, quasi-randomized pilot study to compare the efficacy of two treatment regimens of Traumeel S® with no treatment in reducing post-operative pain. The protocol was approved by the Ethics Committee of Shaare Zedek Medical Center, and all patients gave written informed consent. Thirty consecutive patients aged 18–80 years scheduled for elective *H. valgus* repair between October 2004 and February 2005 were enrolled in the study. Exclusion criteria included participation in another clinical trial within 4 weeks prior to enrollment and inability to comply with the study protocol. Traumeel-ampoules and tablets were supplies free of charge by HEEL Company, Baden-Baden, Germany.

Patient allocation was quasi-randomized. In the first week, all patients scheduled for surgery who met all inclusion and no exclusion criteria were assigned to the control group. In the following week all patients scheduled for surgery were assigned to the "injection only" group, and in the third week all patients were assigned to the "injection + PO" group. This process was

repeated until the predetermined sample size of 30 was reached. The control group received neither additional active treatment nor placebo beyond conventional care. The "injection only" group received an injection of Traumeel (2.2 ml) into the operative incision upon conclusion of surgery. The "injection + PO" group received an injection of Traumeel (2.2 ml) and then Traumeel tablets *per os* three times daily (1 × 3) for 13 days or until pain was "negligible or non-existent" (VAS <3). All operations were performed under local anaesthesia using Bupivicaine 0.5% and lidocaine 1%. Surgery was performed by any two of a permanent staff of three foot-specialists. The operational technique was chosen based solely upon orthopaedic considerations. Patients were released on the day of surgery, and seen at follow-up by the operating surgeon 6 and 13 days after surgery.

After the operation, patients were asked to take only tablets of paracetamol 325 mg with codeine 15 mg (primary oral analgesic) for pain relief. Patients were also given prescriptions for tramadol hydrochloride 100 mg, for use as "rescue" analgesic. At discharge, patients were provided a daily dairy including daily VAS score and daily consumption of analgesics. The VAS scale used was a vertical, graded scale accompanied by faces expressing varying degrees of displeasure alongside the words "no pain", "mild pain", "bothersome pain", "severe pain", "very severe pain", "worst possible pain". Patients were instructed to fill out the diary at the end of each day for 13 post-operative days, recording on the VAS scale the highest level of pain they had experienced at rest during that day, the total amount of primary oral analgesic ingested, and the amount and type of rescue analgesic they consumed. They were instructed to return with the diary to follow-up visits performed on postoperative days 6 and 13. We considered all WHO pain relief ladder levels 1 and 2 oral analgesics [19] as equal for purposes of calculation. Strong opiates (level 3), were arbitrarily counted as equivalent to two non-opiate oral analgesic doses (level 1 or 2).

2.1. Statistical analysis

We compared demographic and baseline clinical values between the three groups using a non-parametric Kruskal–Wallis test for independent samples for means, or a chi-square test for proportions. Results were given as mean ± S.D. for quantitative variables and as frequencies (proportions) for qualitative variables.

We examined the mean VAS score difference between groups, the course of VAS scores during the follow-up period, and the interaction between group and time effects. For this purpose, we used a repeated-measures mixed model with fixed effects of treatment, time and the interaction term of these two variables, and a random subject effect. A heterogeneous autoregressive variance–covariance matrix structure was selected for the repeated measurements since it best fitted our data, based upon both the Akaike's information criterion (AIC) and the Bayesian information criteria (BIC). This structure specifies that on the same patient, observations which are more proximate are more correlated than measures that are more distant and that the variance of VAS scores changes over time. Time was included as a categorical instead of continuous variable in order to avoid assuming a particular form of mathematical relationship between mean change in pain and time. We included all available VAS scores. Baseline (immediately prior to the injection of Traumeel) scores were not available because the patient was still under the influence of the local anaesthesia. Since we could check that baseline demographics were balanced between groups, we assumed that – although it was not a randomized trial – study groups were also comparable with respect to baseline pain. Restricted maximum likelihood procedures were used to estimate and test hypotheses about the parameters. Pairwise comparisons were carried out to compare the single injection group to the control group, the injection + PO group to the control group and the two groups receiving Traumeel. Tukey multiple comparison procedure was used for ensuring control of the overall type 1 error rate.

Mean cumulative analgesic consumption analysis was compared in the different groups by using a non-parametric Kruskal–Wallis test for independent samples. Statistical analyses were done using SAS software for Windows, 8.2 (SAS, Inc., Cary, NC).

3. Results

A total of 30 patients were eligible to participate in the trial. No eligible patients refused. Eleven patients were assigned to the control group, nine to the single injection group and ten to the injection + PO group. The subject characteristics are shown in Table 2. Most participants were female (93%). There were no significant differences among groups in sex, age, type and side of procedure. All 30 patients completed the study and returned for both follow-ups. All patients returned diaries. Sixty-seven percent of the patients filled out the whole 13 VAS scores, with significant differences

Table 2 Demographic and clinical characteristics of the sample population

	Control arm ($n=11$)	Single injection arm ($n=9$)	Injection + PO arm ($n=10$)
Age (mean ± S.D.)	51.3 ± 17.3	58.3 ± 17.5	51.5 ± 15.1
Female, % (n)	100 (11)	89 (8)	90 (9)
Side (% right)	40	57	57
Procedure (% Chevron)	78	78	67

among group (64% in control group, 44% in the single injection group and 90% in the injection + PO group, chi-square test, p-value = 0.001). VAS score repeated measures means for each group are plotted versus days in Fig. 1. The graph shows that from the first day of treatment, the mean pain was less in both groups receiving Traumeel (either single injection or injection + PO) than in the control group. Means for Traumeel groups continued to be lower than control means for subsequent days (except for the injection + PO group at day 2). Moreover, the means for both Traumeel groups are essentially the same during the whole period of study. In all patients, regardless of the treatment received, mean VAS scores significantly decreased over time ($p < 0.0001$). There was a significant difference in post-operative pain between the three groups ($p = 0.02$). Mean VAS scores were significantly lower in the single injection group and in the injection + PO group than in the control group ($p = 0.02$ and 0.05, respectively) while there was no significant difference between the single injection group and the injection + PO group. The interaction between time and group was significant ($p < 0.0001$) indicating that the magnitude of the differences between groups was not constant over time.

Similar levels of consumption of analgesics were observed in the single injection group (21 ± 16) and the injection + PO group (22 ± 19). Although the total consumption of analgesics appeared greater in the control group (37 ± 28) as compared to the groups receiving Traumeel, the difference was not statistically significant (Fig. 2, Kruskal–Wallis test, $p = 0.2$). The largest magnitude of the difference was observed during the first week (Fig. 3). Patients took a large variety of oral analgesics in addition to, or in place of the intended primary oral analgesic. Three patients took level 3 opiates or opiate analogues. Two patients in the "injection + PO" group took oxycodone for 2 days each. One patient in the control group took either oxycodone or tramadol for 11 days. Five courses of antibiotics were prescribed

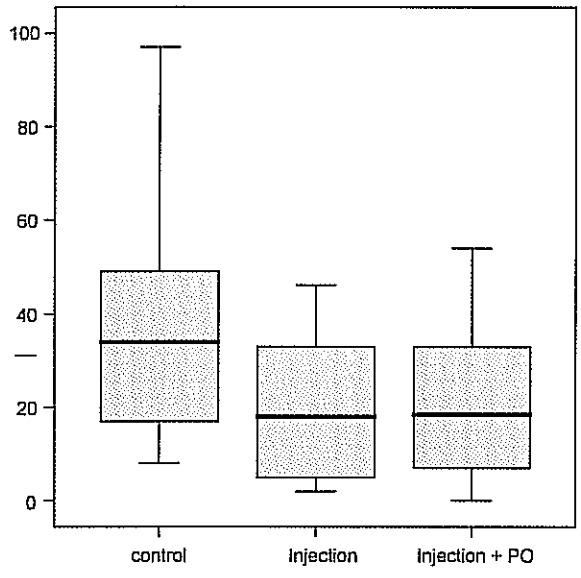

Fig. 2 Total consumption of analgesics (number of pills) according to study group.

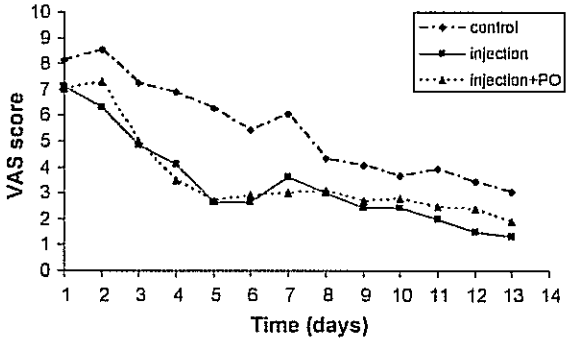

Fig. 1 Pain repeated measures means according to study group.

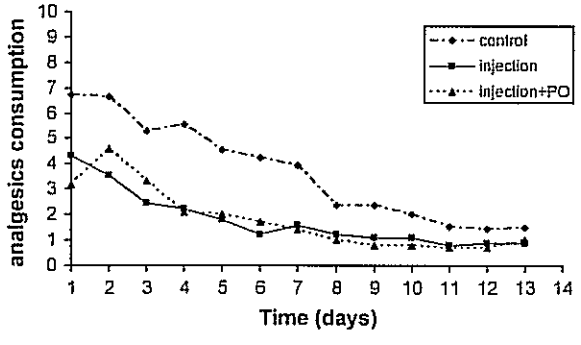

Fig. 3 Mean daily analgesic consumption (number of pills) according to study group.

at 6-day follow-up based upon clinical suspicion of wound infection; three in the control group, and one each in the 'injection only' and 'injection + PO' group. No side effects related to the study medications were reported.

4. Discussion

We performed a pilot study to examine the efficacy of two regimens of the homeopathic preparation Traumeel S® in minimizing post-operative pain and analgesic consumption after surgical correction of *H. valgus*. Despite the small sample size, pain was significantly reduced in both Traumeel groups as compared with no treatment, and analgesic consumption was lower but did not reach statistical significance. There was no statistically significant difference in pain between the two arms receiving Traumeel.

The biological mechanism of action of miniscule doses remains unexplained. Nor does this study allow us to tease apart the effects of the individual components or their various combinations. A much larger study would be necessary for such an undertaking. Some of the ingredients are regarded by homeopaths as anti-inflammatory (Belladonna, Aconitum, Mercurius, Hepar, Chamomilla) and some muco-protective (Calendula, Hamamelis). Arnica a leading homeopathic remedy for trauma. Arnica, Calendula, Hamamelis, Milefolium are considered anti-haemorrhgagic. Echinacea ang. and Echinace purp. are considered immunostimulant. Hypericum is used in cases of neural injury. The sample size was also too small to differentiate the effects of the two dosage regimens. Unsurprising from a homeopathic standpoint is the long term activity of a single injection. Many homeopaths prescribe their medications on a weekly or monthly basis.

The study has several limitations: first, the study was open, potentially biasing assignment and outcome assessment. Secondly, the study was not formally randomized. However, comparing baseline variable distributions, we found that the three arms were similar with regard to all variables which we believe could influence treatment outcome. Third, we used a "no treatment" control group. This type of control allowed to discriminate between pain reduction due to the effect of Traumeel from natural reduction of pain over time. However, since patients in this arm were not given any placebo, we cannot affirm that we totally eliminated the placebo effect of Traumeel. The choice of a "no-treatment" control was driven by the desire to avoid placebo injection in those groups not receiving active medication. We did not use an active control group since patients were allowed to take primary oral analgesics to relieve pain if needed.

In spite of the limitations of this pilot study, we demonstrated a significant reduction in post-operative pain in the treatment groups, using a homeopathic complex medication. These results would appear to warrant further study of this complementary treatment for post-operative pain. This small pilot study has also provided preliminary data on which to base a larger, randomized double-blind, placebo-controlled study examining the reduction of post-operative pain and use of analgesics. Such a study is now underway at the Shaare Zedek Medical Center in Jerusalem.

Conflict of interest

The authors declare no conflict of interest, financial or other, regarding any material in this paper.

Acknowledgement

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