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Postoperative analgesic efficacy of dexamethasone sodium phosphate versus triamcinolone acetonide in bunionectomy: A prospective, single-blinded pilot randomized controlled trial

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Background: Corticosteroids are often administered via injection preoperatively to reduce post-operative inflammation and pain. Despite their wide anecdotal application in clinical practice, there are no current guidelines pertaining to appropriate corticosteroid selection. This study aims to investigate and compare the efficacy of dexamethasone sodium phosphate (DSP) and triamcinolone acetonide (TA) in postoperative pain management following hallux valgus surgery.
Methods: A randomized, prospective, single-blind study comparing preoperative DSP versus TA injections was conducted on 20 participants who were undergoing elective hallux valgus surgery. Postoperative pain scores (pain intensity and pain interference with daily activities) were assessed with Brief Pain Inventory Short Form (BPI-sf) questionnaire at the time of first postoperative oral analgesic consumption or 14 days after surgery if no analgesics were required. Differences in clinically significant pain scores were also assessed with prospectively defined response criteria.
Results: The difference in mean for pain intensity and pain interference were found to be significantly lower for TA group as compared to DSP group ($p = 0.006$ and $p = 0.001$) respectively. Significant difference was also observed in the proportion of participants who reported absence of postoperative pain scores between DSP and TA groups ($p = 0.025$ and $p= 0.006$) respectively. However, there were no significant differences between time to postoperative analgesia consumption and proportion of participants requiring oral analgesia ($p>0.05$).
Conclusions: This study provides preliminary evidence suggesting that TA is associated with lower pain scores compared to DSP. Further research is required to establish the effects of TA and DSP in managing postoperative pain following hallux valgus surgery.

Key words: Hallux valgus; Bunionectomy; Corticosteroid; Triamcinolone Acetonide; Dexamethasone Sodium Phosphate; Podiatry; Post-operative; Pain; Analgesics

Over the decades, pain continues to remain as one of the main postoperative adverse outcomes that cause distress to patients [1-5]. While great advances in the use of medications for postoperative pain control has been made, numerous studies have indicated continued undertreatment of pain [1-5]. A 2003 national survey conducted by Apfelbaum et al. [6] showed evidence of this ineffectiveness in pain management, where approximately 80% of patients who experienced acute pain immediately after surgery.

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Of these, 86% described their pain as being moderate to severe in intensity [6]. A recent study conducted by Gan et al. [7] revealed similar findings, illustrating the lack of progress in postsurgical pain management.

Current attempts to reduce post-operative pain include the use of several agents, categorized as opioids and nonopioid analgesics [1,3,4] Amongst these, opioid analgesics are used as the conventional first-line approach to postoperative pain management [2,3]. Its use, however, has been associated with serious adverse effects such as respiratory depression, constipation, sedation and postoperative nausea and vomiting [1,8]. As such, multimodal analgesic regimens that use non-opioid analgesics to facilitate lower dosing of opioids are gradually replacing plain opioid analgesics in postoperative pain management [8]. However, serious systemic side effects associated with multimodal analgesic regimens can still occur. Hence, there is still a need for further reductions in opioid intake.

Corticosteroids are a group of hormones that elicit analgesic effects through phospholipase A2 inhibition [9]. They prevent formation of arachidonic acid and subsequent inflammatory mediators that are responsible for causing inflammation, edema and pain [9]. Its analgesic properties have been well demonstrated in the context of oropharyngeal and maxillofacial surgeries [9-11]. Their value as a therapeutic approach to postoperative pain relief for podiatric surgery is however, not well explored.

The few studies that have reported corticosteroid use in podiatric surgeries have identified dexamethasone sodium phosphate (DSP) to be a frequently administered postoperative analgesic agent [12-15]. DSP, a synthetic and soluble adrenocortical steroid, is a rapid short-acting preparation of dexamethasone that has been profoundly used in conjunction with local anaesthetics to minimize acute pain and inflammation after foot and ankle surgeries [12-15]. A study by Curda [14] demonstrated the effectiveness of DSP-bupivacaine combination over bupivacaine alone in reducing postoperative pain at 24 hours ($p < 0.0001$) and 4 to 7 days after surgery ($p = 0.0004$).

Bryant et al. [15] illustrated the opioid sparing effects of DSP by demonstrating a marked reduction in narcotics and oral analgesics intake following DSP injections, as compared to its control. Miller and Wertheimer [13], however, did not find any improvements in postoperative pain outcomes 48 – 72 hours after the use of DSP.

It is to note that the clinical trials described previously were published before year 2000. There is no recent literature which investigates the efficacy of DSP as postoperative analgesia following hallux valgus surgery. Therefore, its effectiveness in reducing pain after podiatric surgery remains debatable. A longer acting corticosteroid which provides extended and uninterrupted pain relief can greatly improve postoperative pain management. Optimal pain relief will in turn minimize patient discomfort, decrease the need for postoperative oral analgesic, facilitate early mobilization and optimize functional recovery [4].

Triamcinolone acetonide (TA), normally formulated as a crystalised suspension, is a relatively insoluble, intermediate acting adrenocortical steroid with a long duration of action [16]. Synergistic use of TA alongside mixture of bupivacaine and epinephrine has demonstrated longer pain relief, better joint mobility and significant opioid sparing effect following knee surgeries compared to the mixture itself [16-20]. The use of TA in podiatric surgery, although popular, has not been investigated.

With the above in mind, further research is required to support the use of corticosteroids in podiatric surgery and determine the most appropriate corticosteroid to alleviate postoperative pain. The aim of this research was therefore to assess and compare the postoperative analgesic efficacy of DSP and TA in participants undergoing hallux valgus surgery. The null hypothesis was that TA would exhibit the same analgesic efficacy as DSP in hallux valgus surgery.

Methods

Ethics

This study was approved by the Human Research Ethics Committee, University of Western Australia, Australia (File Reference: RA/4/1/6631).

Study design and participants

This participant-blinded randomized controlled trial compared the efficacy of DSP with TA in alleviating postoperative pain in participants undergoing hallux valgus surgery, over 14 days. As this pilot study was exploratory in nature and undertaken for feasibility, no sample size calculations were performed. We estimated that 20 participants with similar demographics would represent an adequate sample to inform future trial design and generate appropriate study hypotheses.

Recruitment

From May to December 2014, 20 healthy participants (2 males, 18 females) fulfilling the enrolment criteria and providing informed consent were recruited at the University of Western Australia Podiatric Surgery Clinic. Participants were eligible for the study if they were above 18 years old and undergoing surgical correction of hallux valgus facilitated through the University of Western Australia Podiatric Surgery Clinic. Participants were excluded from the study if they had, 1) cognitive impairment, 2) intellectual disability, 3) physical disability or mental illness, 4) allergy or hypersensitivity to any corticosteroids, 5) systemic viral and fungal infections, 6) allergy or hypersensitivity to paracetamol or codeine, 7) diabetes mellitus, 8) chronic renal failure, 9) inflammatory arthritis and any other forms of immunodeficiency, and 10) taking medications that could interact with DSP or TA at the time of study.

Randomization and blinding

Participants were randomly allocated to receive either DSP (4mg/mL) or TA (10mg/mL). Randomization allocation was prepared using simple randomization coin tossing method prior to participant recruitment. The podiatric surgeon administering the corticosteroids was blinded to the intervention allocation until the day of hallux valgus surgery. Corticosteroid allocation was revealed to the podiatric surgeon by a study investigator prior to the surgery.

The study design was only single-blind due to the difference in solubility of the two corticosteroids, which caused an inevitable color difference that could be detected by the podiatric surgeon during injection. All participants remained blinded to the intervention group assignment.

Corticosteroids

The DSP injection used was DBL™ dexamethasone sodium phosphate (Hospira Inc., Australia), a sterile solution containing 4 mg dexamethasone phosphate, 8 mg creatinine, 10 mg sodium citrate, and water for injections quantity sufficient to 1 ml. The TA used was Kenacort ® -A 10 (Aspen Pharmacare, Australia), a sterile solution containing 10 mg triamcinolone acetonide, 6.6 mg sodium chloride, 15 mg benzyl alcohol, 6.4 mg carmellose sodium, 0.4 mg polysorbate 80, and water for injections quantity sufficient to 1 ml. pH was adjusted using sodium hydroxide and hydrochloride acid for both solutions.

Protocol

The corticosteroid injection was administered to the participants pre-operatively, in combination with 5mL of 0.75% Naropeine. The amount injected was divided equally and infiltrated on the dorsal, medial, plantar and lateral aspects of the first metatarsal, in a Mayo block fashion proximal to the surgical site. The dose injected was based upon previous experiences of the podiatric surgeon and falls within the recommended dose ranges for soft tissue corticosteroid injections. The hallux valgus surgery was then performed following the standard University of Western Australia protocol for Austin bunionectomy.

After the procedure, dressings for the surgical site were applied uniformly by the same surgeon to eliminate the risk of increased postoperative pain secondary to a tighter bandage on one participant than on the other. Participants were also advised to minimize weight-bearing activities to promote healing. All participants were given postoperative oral analgesic medication, which contained the active ingredients paracetamol and codeine, as part of the University of Western Australia Podiatric Surgery Clinic's standard postoperative care procedure. Participants were encouraged to take the oral analgesic medication when pain was perceived as intolerable. Intolerable pain was defined as pain scores greater than 3/10 on a numerical rating scale (range 0-10).

Primary Outcomes	Pain intensity
	Pain interference with daily activities
	Presence of clinically significant pain
Secondary Outcomes	Time (days) to post-operative oral analgesia
	Proportion of participants who consumed post-operative analgesic medication within each treatment group

Table 1 Primary and secondary outcomes of study.

Outcome measures

The primary outcomes of this study were pain intensity, pain interference with daily activities and presence of clinically significant pain. These postoperative pain scores were assessed using the Brief Pain Inventory-Short Form (BPI-SF) questionnaire. The BPI-SF is a validated, 15-item questionnaire that rates pain over the last 24 hours and the degree to which it interferes with activities on a 0 to 10 scale [21]. In this study, pain severity was measured as worst pain in the last 24 hours (i.e. item 3 of the BPI-SF) and the pain interference score as the mean score of all seven BPI-SF items (i.e item 9A-G) assessing interference of pain with activities of daily living. All measurements were done based on recommendations by Cleeland [22]. For the purpose of pain intensity analyses, the presence of clinically significant pain was defined as a score of 4 or more on BPI-SF item 3, and for the pain interference analyses, as a mean score of 4 or more on the BPI-SF pain interference scale.

Secondary outcomes of this study include time taken to postoperative oral analgesic consumption and proportion of participants requiring postoperative oral analgesia. All secondary outcomes were recorded with a patient logbook and analyzed prospectively as per analysis plan. Primary and secondary outcomes were outlined in Table 1.

Participants were instructed to complete a baseline questionnaire covering demographic information prior to the hallux valgus surgery. The self-administered BPI-SF questionnaire was completed at the time to first postoperative oral analgesic consumption or 14 days after surgery if no postoperative oral analgesics were required. Participants were also instructed to record the date of the first oral analgesic consumed after surgery on logbook. All outcome measures were obtained 14 days after the hallux valgus surgery.

Statistical analysis

All statistical analyses were performed using International Business Machines Statistical Package for the Social Sciences Statistics software version 22.0 (SPSS Inc., Chicago, Illinois).

Demographic and outcome variables were described by using means and standard error of means for continuous variables and percentages for categorical variables by treatment group. The data were explored for normality using the Shapiro-Wilk test prior to inferential analysis.

Two-sample t tests were used to compare between-group differences for age, worst pain level and mean pain interference. Mann-Whitney U test was used to compare time to postoperative oral analgesic consumption. Lastly, Pearson's chi-squared tests or Fisher's exact test were used to compare gender, sides, the absence or presence of clinically significant pain and pain interference with daily activities, and proportion of participants who consumed postoperative analgesic medication within each treatment group.

The significance for all tests was set at p-value < 0.05.

Results

Demographics

Between May and December 2014, a total of 20 participants were recruited and randomly assigned to two groups: 10 participants received DSP (Group D) and the remaining 10 received TA (Group T). There were 1 male and 9 female participants in each group, with an average age of 48.2 ± 5.1years in group D and 62.1 ± 4.1 years in Group T. Age difference between group D and T was statistically significant ($p = 0.048$). There were no significant differences in other baseline demographics between the two treatment groups ($P > 0.05$) (Table 2).

	Group D (n=10)	Group T (n=10)	P-value*
Gender (M/F)	1/9	1/9	P= 0.763
Age (y)			
Mean ± Standard Error of Mean, (range)	48.2 ± 5.1, (22-71)	62.1 ± 4.1, (31-76)	**P= 0.048**
Sides (Unilateral/Bilateral)	4/6	6/4	P= 0.371
*P values were based on two-sample t tests comparing differences in between-group means. Pearson chi-squared or Fisher's exact test used to compare the proportions between categorical data. Bolded values indicate statistical significance ($P < 0.05$).			

Table 2 Clinical demographic details of the study groups.

Severity item			
	Group D (n=10)	Group T (n=10)	P-value*
Mean (SEM) worst pain level	5.5 (0.7)	2.8 (0.6)	**P= 0.006**
Pain interference items			
Mean (SEM) pain interference with daily activities	4.3 (0.6)	1.3 (0.5)	**P=0.001**
• Abbreviation: BPI-sf, Brief Pain Inventory-short form; SEM, standard error of mean • *P values were based on two-sample t tests comparing differences in between-group means • Bolded values indicate statistical significance ($P < 0.05$). • Pain scale of 0–3 indicates the absence of clinically significant pain and 4–10 indicates presence of clinically significant pain			

Table 3 Mean (SEM) postoperative BPI-SF questionnaire score.

Severity item					
	Group D (n=10)		Group T (n=10)		P-value *
	Absent	Present	Absent	Present	
Worst pain	2/10 (20.0%)	8/10 (80.0%)	7/10 (70.0%)	3/10 (30.0%)	**P=0.025**
Pain interference items					
Mean pain interference with daily activities	3/10 (30.0%)	7/10 (70.0%)	9/10 (90.0%)	1/10 (10.0%)	**P=0.006**
• * P values were based on Pearson's chi-squared or Fisher's exact test comparing differences in between group • Bolded values indicate statistical significance ($P < 0.05$). • Pain scale of 0–3 indicates the absence of clinically significant pain and 4–10 indicates clinically significant pain is present					

Table 4 Pain severity and interference with daily activities (absent vs present).

	Mean (SEM)	P-value*
Group D	0.4 (0.2)	P=0.240
Group T	3.2 (1.8)	
• Abbreviation: SEM, standard error of mean • *P values are based on Mann-Whitney-U tests comparing differences in between-group means		

Table 5 Time (day) to postoperative analgesic medication.

Table 6. Proportion of participants who consumed post-operative analgesic medication within each treatment group			
	Group D	Group T	P-value*
Total (%)	10/10 (100)	8/10 (83.3%)	P= 0.136
• Abbreviation: SEM, standard error of mean * P values are based on Pearson's chi-squared or Fisher's exact test comparing differences in between group			

Table 6 Proportion of participants who consumed postoperative analgesic medication within each treatment group.

Mean pain severity and pain interference

Participants in Group T reported significantly lesser pain level and pain interference level as compared to Group D (p = 0.006 and p = 0.001 respectively) (Table 3). In addition, the mean scores for worst pain and pain interference level observed in Group T were lower than 3, in contrast to Group D, which reported mean values of 4 and above.

Absence and presence of clinically significant pain and interference with daily activities

Greater proportions of participants in Group T reported absence of clinically significant postoperative pain and pain interference compared to Group D (p = 0.025 and p = 0.006 respectively) (Table 4).

Time to postoperative analgesic medication consumption

There were no significant differences between Group T and Group D in the number of days before consumption of analgesia (p = 0.240) (Table 5).

Proportion of participants who consumed postoperative analgesic medication within each treatment group

There were no significant differences between Group T and Group D in the proportion of participants who consumed postoperative analgesics within each treatment group (p=0.136) (Table 6).

Discussion

To our knowledge, the current study represents the first investigation aimed at exploring and comparing the postoperative analgesic efficacy of DSP and TA in hallux valgus surgery. The proposed clinical benefits of TA derived from its insoluble nature was allowing prolonged uptake of TA from its injection site [16-20,23]. As a result, TA remains in tissues for an extended period to provide sustained anti-inflammatory action [16,20,23]. Duration of action of TA is therefore longer than the soluble DSP, lasting up to 2-3 weeks, as compared to only 36-72 hours with soluble DSP. [16,19,20,23,24]

In this pilot study, TA was found to favorably affect measures of postoperative pain symptoms (patient-reported pain severity and mean pain interference with daily activities) in hallux valgus surgery compared to DSP. Notably, more than half of participants in TA group considered the pain severity and interference with daily activities to be not clinically significant. This observation is in contrast with the effects of DSP, where more than half of the participants reported clinically significant pain and pain interference with daily activities (Table 4). These results suggest that postoperative oral analgesic medication may not be required when using TA in hallux valgus surgery. On the other hand, its use may be required when using DSP.

Although the effect of TA has not been investigated in previous podiatric literatures, there are evidences that TA can substantially decrease pain scores, postoperative oral analgesic intake, and improve range of motion post-operatively following knee surgeries. Wang et al. [16] found that TA could provide significant pain relief 6 to 24 hours post-operatively ($p<0.05$ to $p<0.01$) as compared to placebo. In addition, none of the patients from TA group required rescue analgesia as compared to 53% of patients from the placebo group ($p <0.001$). Pang et al. [19] found significant reductions in pain ($p = 0.014$ at 12 hours, $p = 0.031$ at 18 hours and $p = 0.031$ at 24 hours) and better range of motion of knee ($p = 0.023$ at three months) post-operatively in patients receiving TA, compared to a control group without TA. Kwon et al. [17] reported lower pain intensity in TA group immediately ($p= 0.021$) and for up to 7 days post operatively ($p>0.05$) following knee arthroplasty. This finding was accompanied with earlier functional recovery ($p=0.013$) as compared to the control group. Therefore, our findings support the hypothesis that a longer acting corticosteroid can provide adequate, extended and uninterrupted pain relief.

Although TA achieved greater reductions of postoperative pain when compared to DSP, no significant differences were observed between DSP and TA in the time to postoperative oral analgesic consumption and proportion of participants requiring postoperative analgesia. Several possible explanations exist as to why the results were inconsistent. Even though a longer duration of action was observed in TA group compared to DSP as represented by extended time to postoperative oral analgesia, the mean difference of 3 days does not justify the theoretical duration of action of TA (14-21 days). Most participants receiving TA were seen to administer postoperative oral analgesic medications on postoperative day 0 or day 1 despite adequate analgesia (pain scores lesser than 4). One probable reason for the pre-emptive administration of oral analgesics is the fear of pain, thus the use of oral medication prophylactically as a preventative measure rather than a pain relief. Individual differences in pain sensitivity must also be considered as plausible contributing factor. Lastly, the theorized duration of action of TA might not be adequately demonstrated when injected in small quantities around the hallux.

All of the above factors can in turn correlate with the overall increase in the proportion of participants who consumed postoperative oral analgesics. The null hypothesis that TA would exhibit the same analgesic efficacy as DSP in hallux valgus surgery was therefore partially rejected.

The relationship between age and intensity of postoperative pain remains controversial. Our study showed significant difference in age group between the two treatment arms. While several studies have suggested higher postoperative pain in a younger age population [25,26], some have failed to show any correlation [27-30]. Gagliese et al. [29] had proposed that the controversy may be secondary to a series of confounding factors which indirectly affect pain intensity across age groups. Nonetheless, all of the studies mentioned above included a wide variety of surgeries under their methodologies which can contribute to multiple confounders. In addition, there is no current literature which identifies age as a predictive factor for postoperative pain following foot and ankle surgery.

On a side note, many participants reported taking other pain-relief medications during intervention period rather than the recommended oral analgesics. Upon further investigation, opioid-related side effects such as nausea, vomiting and constipation were identified to be the main reasons associated with non-compliance. While these findings did not affect study outcomes, they correlate to previous literatures which highlighted the importance of non-opioid analgesia to improve quality of postoperative recovery [1,3,8]. Therefore, future efforts require better study designs to enable a more accurate assessment and comparison of opioid sparing effect between the two corticosteroids.

The findings of this study should be interpreted in light of its limitations. Firstly, the absence of a placebo group in this study is a limitation, but withholding analgesia for a painful procedure raises ethical concerns. Secondly, the small study population limited the power and reliability to detect the mean differences between the corticosteroids. Further studies using larger sample sizes are therefore warranted.

Thirdly, as inter-participant comparison of the two corticosteroids was done in this study, individual participant tolerance to pain was a variable and pain scores might not accurately reflect the general population. In order to increase the accuracy of the study, intra-participant comparison of the two corticosteroids should be conducted. We propose preoperative administration of different corticosteroids on each foot for patients with bilateral hallux valgus to minimize inter-participant variables. The sex ratio of the participants in this study was strongly skewed towards the female gender. Therefore, results obtained may possess certain biases towards female patients. We suggest the use of a sample size with equal sex ratio to counter this problem. Lastly, due to time constraints, we were unable to investigate for any possible long-term side effects associated with corticosteroid use. As such, we propose having a longer follow-up duration in future studies to explore into the probability of these complications.

Conclusion

This is the first randomized, prospective, single-blind pilot study investigating and comparing the postoperative analgesic efficacy of DSP versus TA in hallux valgus surgery. In this study, TA was associated with lower pain severity and pain interference scores compared to DSP, suggesting its use as a promising postoperative analgesia in relieving pain following hallux valgus surgery. However, large, adequately powered studies are needed before the effects of TA and DSP in hallux valgus surgery can be established definitively.

Abbreviations

DSP: Dexamethasone sodium phosphate; TA: Triamcinolone acetonide; BPI-SF: Brief Pain Inventory-Short Form

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