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Role of anti-oxidant (vitamin-C) in post-operative pain relief in foot and ankle trauma surgery: A prospective randomized trial

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ABSTRACT

Background: Post-operative pain may adversely affect a patient's quality of life. Studies have shown that vitamin C, being an anti-oxidant and neuro-modulating agent, can help to reduce pain in a variety of clinical settings. The objective of this randomized controlled trial was to assess the effectiveness of vitamin C in reducing post-operative pain, analgesia requirements and improving functional outcome.
Methods: Patients with isolated foot and ankle trauma, who had undergone surgery, were randomly assigned to receive either vitamin C 500 mg or a placebo tablet twice a day. VAS score, analgesia requirement and functional outcome were assessed during their regular follow up. Results were compared and analyzed at the end of 3 months.
Results: The group which received vitamin C, showed improvement in VAS score at the end of second and sixth week of follow up, reduced analgesia requirements and improved functional outcome as compared to the placebo group.
Conclusions: This study shows that the supplementation of vitamin C in patients undergoing surgery for foot and ankle trauma helps to reduce analgesic requirements, improve VAS scores and achieve better functional outcome.

1. Introduction

Post-operative pain, an unfortunate and unwanted consequence of surgery, remains a major challenge for health care providers [1,2]. Inadequate pain relief after foot and ankle surgery can adversely affect functional outcome and patient satisfaction because of increased hospital stay, slower rehabilitation and delayed return to regular activities [1–4]. Routinely used treatment modalities to reduce severe post-operative pain are nerve blocks and multimodal analgesia (i.e. combination of drugs and/or techniques). These therapeutic options have substantial limitations and may have problematic side effects.

Nerve blocks being invasive, carry the risk of nerve injury and provide only short term benefits. There are conflicting reports regarding the use of gabapentin in post-operative pain relief; some studies demonstrate reduction, whereas others describe no effect [5]. Gabapentin has also been shown to negatively affect bone healing in rat models [6]. Opioids are potent analgesics but are associated with side effects like nausea, vomiting, constipation, dizziness, and respiratory depression [7,8].

Vitamin C is water-soluble, found throughout the body and is especially highly concentrated in the brain [9]. Being an anti-oxidant, it limits the tissue injury and acts as a neuro-protective and a neuro-modulating agent [10]. Vitamin C is also necessary for normal growth, development and formation of collagen, the latter being important for the healing of skin and scar tissue, blood vessels, ligaments and tendons [11]. The potential use of vitamin C supplementation as an adjuvant for managing post-operative pain has been explored in a literature review by Kiabi et al. [12]. A few other studies have shown that vitamin C supplementation significantly reduces the pain caused due to hip and/or knee osteoarthritis and spontaneous pain experienced by patients with post-herpetic neuralgia [13,14]. A recent study has shown that oral supplementation of vitamin C has significantly reduced the acute pain and consumption of morphine after laparoscopic cholecystectomy [11].

Keeping in mind the benefits of vitamin C, we hypothesized that it would also help to reduce post-operative pain and hence

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improve the functional outcome. With this objective, a randomized controlled trial was planned to assess the effectiveness of vitamin C in reducing post-operative pain, analgesia requirements and improving functional outcome in patients undergoing surgery for foot and ankle trauma.

2. Materials and methods

Healthy patients between 18–60 years of age with isolated foot and ankle trauma (closed fracture) who presented to the orthopedics emergency were enrolled for the trial after a written and informed consent. Patients with renal calculi, diabetes mellitus, genetic disorders like glucose–galactose malabsorption, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, taking fluphenazine or multivitamin supplementation, pregnant or breast feeding females, with prior history of injury to the affected ankle or foot and with open fracture were excluded from the study. Prior institutional ethical committee approval was taken for the study.

All the patients underwent appropriate surgery according to the type of fracture under spinal anesthesia. The approaches and fixation methods used for each fracture type are mentioned in Table 1. Spinal anesthesia was given using 2.5–3 ml bupivacaine according to the height and weight of the patient. Patients were randomly allocated to vitamin C or placebo group pre-operatively (group assignments were determined by a computer-generated number sequence and were contained in sequentially numbered opaque envelopes to ensure blinding). Patients, researchers and physicians were blind to the medication given; only the pharmacist was in possession of the allocation code. From post-operative day one, patients received a daily dosage of 500 mg of vitamin C or a placebo tablet twice a day for 6 weeks. Both vitamin C and placebo tablet were similar in size, color and shape. In addition, all the patients were also given diclofenac sodium 75 mg twice a day for 5 days for acute pain relief, to reduce swelling and afterwards as and when required. They were asked to keep a record of the number of tablets of diclofenac sodium consumed for 6 weeks. The amount of diclofenac sodium consumed for the next 6 weeks was calculated.

All the patients were assessed and evaluated clinically and radiographically on follow up at first, second, sixth week and at 3 months post-operatively in outpatient department. Pain was measured using a 10 point visual analogue scale (VAS). Patients marked the scale to indicate the degree of pain felt at rest and with use of the foot and ankle, with 0 being no pain and 10 being maximal pain, at every follow up visit. The amount of analgesia used in 6 weeks was measured in grams. The functional outcome score was measured at the end of 3 months by American Academy of Orthopaedic Surgeons (AAOS) "foot and ankle outcome instrument (FAI)" core scale [15]. The FAI core scale consists of 2 components: standardized and normative scores. Standardized scores were calculated so that a "0" represents a poor outcome/worse health, while "100" was the best possible outcome/health. Normative scores were calculated so that higher scores indicate better functioning. All scores were referenced to the general/healthy population mean normative score of 50.

2.1. Statistical analysis

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables were presented as mean ± SD or median if the data was unevenly distributed. Categorical variables were expressed as frequencies and percentages. The comparison of normally distributed continuous variables between the groups was performed using Student's t-test. Nominal categorical data between the groups was compared using Chi-squared test or Fisher's exact test as appropriate. Non-normal distribution continuous variables were compared using Mann–Whitney-U test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference. Interpretation and analysis of data was done by paired t-tests.

3. Results (Tables 2 and 3)

After all the observations were made, allocation codes were opened, the data was compiled according to the groups and analysis was performed. Patients who received the placebo were referred to as group A, while those receiving vitamin C were called group B. There were 30 patients in each group. The distribution of fracture patterns in both the groups is shown in Table 2. The mean age of group A (placebo) patients was 40.10 ± 8.81 (24–58) years and that of group B (vitamin C) was 37.53 ± 11.49 (20–60) years, the difference was not statistically significant ($p = 0.336$). There were 10 female and 20 male patients in group A (placebo) whereas 5 females and 25 males in group B (vitamin C), the difference was not statistically significant ($p = 0.136$). The body mass index (BMI) of patients of group A (placebo) was 29.50 ± 5.27 (20–38) kg/m^2 whereas BMI of group B (vitamin C) was 28.45 ± 4.81 (19.4–37) kg/m^2, which was comparable ($p = 0.425$) in both the groups.

Table 2
Distribution of fracture types among the groups.

Type of fracture	Group A (placebo)	Group B (vitamin C)	*p*-Value
Bimalleolar ankle fracture	15	16	0.636
Isolated medial malleolus fracture	4	6	
Isolated lateral malleolus fracture	4	4	
Trimalleolar fracture	4	2	
Shaft metatarsal fracture (single)	2	0	
Shaft metatarsal fracture (double)	0	1	
Calcaneum avulsion fracture	1	1	
Total	30	30	

Table 1
Approach and fixation methods used.

No.	Fracture	Approach	Incision	Structures protected	Fixation
1	Medial malleolus	Medial approach	Anteromedial incision	Great saphenous vein and Saphenous nerve	4.5 mm partially threaded cancellous screws/tension band wiring
2	Lateral malleolus	Lateral approach	Longitudinal incision along posterior margin of fibula	Sural and superficial peroneal nerve	One third tubular plate
3	Bimalleolar	1 and 2	1 and 2	1 and 2	1 and 2
4	Trimalleolar	1,2 and anterior approach	Anterior midline vertical incision	Anterior tibial nerve and artery	4.5 mm partially threaded cancellous screw
5	Avulsion fracture calcaneum	Posteromedial approach	Longitudinal incision midway between medial malleolei and achilles tendon	Posterior tibial artery and nerve	6.5 mm partially threaded cancellous screw
6	Metatarsal	Closed reduction	–	–	K-wire fixation

Table 3
Distribution of different variable and outcome among the groups.

		Group A (placebo)	Group B (vitamin C)	p-Value
Age (Years)		40.10 ± 8.81	37.53 ± 11.49	0.336
Gender	Male	20	25	0.136
	Female	10	5	
Body mass index (BMI)		29.50 ± 5.27	28.45 ± 4.81	0.425
Injury-surgery interval (days)		1.80 ± 0.925	1.67 ± 1.028	0.599
Tourniquet time (in minutes)		63.67 ± 21.533	62.50 ± 20.834	0.832
Surgery time (in minutes)		78.17 ± 22.263	76.33 ± 22.778	0.754
VAS score	1st Wk	6.97 ± 1.40	6.37 ± 1.45	0.109
	2nd Wk	3.13 ± 1.74	1.83 ± 1.91	0.008
	6th wk	0.63 ± 0.93	0.07 ± 0.254	0.003
Dose of analgesia (gm)		5.70 ± 1.06	3.41 ± 1.05	0.002
FAI core scale	Standadized mean	61.90 ± 9.11	71.87 ± 3.95	<0.001
	Normative score	25.33 ± 6.23	32.67 ± 3.12	<0.001

The injury surgery interval, tourniquet time and time taken to perform surgery were comparable in both the groups ($p > 0.05$).

The visual analogue score (VAS) calculated at one week follow-up was 6.97 ± 1.40 in group A and 6.37 ± 1.45 in group B, the difference between the two groups was statistically insignificant ($p = 0.109$). The VAS score at second and sixth week follow up was 3.13 ± 1.74 and 0.63 ± 0.93 in group A and 1.83 ± 1.91 and 0.07 ± 0.254 in group B respectively. There was a statistically significant difference of VAS score between the two groups at second and sixth week follow-up ($p = 0.008$ & 0.003 respectively), group B scores being significantly lower than group A scores.

The mean amount of analgesia used at the end of 6 weeks, in group A (placebo) was 5.70 ± 1.06 (3–8.2) g and in group B (vitamin C) was 3.41 ± 1.05 (1.3–6.1) g. The difference in terms of analgesia consumed between the two groups was statistically significant ($p = 0.002$), with group A consuming significantly more analgesia.

The functional outcome was assessed at the end of 3 months. The average FAI core scale-standardized mean in group A (placebo) was 61.90 ± 9.11 (36–78) and in group B (vitamin C) was 71.87 ± 3.95 (64–78) and the difference was statistically significant ($p < 0.001$).

The average FAI core scale — normative score in group A (placebo) was 25.33 ± 6.23 (12–65) and in group B (vitamin C) was 32.67 ± 3.12 (27–38) and difference was statistically significant ($p = 0.001$).

As all the patients included in the study underwent surgery, so no patients were lost to follow-up. There was no complication from the high dose of vitamin C. None of the patients in either group developed complex regional pain syndrome. All the fractures healed well.

4. Discussion

This prospective, randomized, double blinded trial has shown that the use of vitamin C decreases the amount of pain and analgesia required following foot and ankle surgery. This is also associated with an improved functional outcome.

Vitamin C (ascorbic acid) is an organic acid with antioxidant properties. It is required for a number of biochemical reactions, mostly involving oxidation [16]. Vitamin C is also necessary for normal human growth and development. At the tissue level, a major function of ascorbic acid is related to the synthesis of intercellular substances, including collagen, the matrix of bone, intercellular cement of the capillary endothelium and as a neuro-protective and neuro-modulating antioxidant [10].

Trauma or injury to a part of body leads to consumption of large quantities of vitamin C from the body reserves. Long et al. demonstrated low plasma levels of ascorbic acid following trauma and infection [17]. Although the site of action for vitamin C as an analgesic is not yet fully understood, vitamin C supplementation in the range of 0.5–3 g/d has been shown to be effective in reduction of pain in a variety of different clinical settings [11–14,18–24]. In our study, the VAS score was significantly lower in the group of patients who received vitamin C at the second and sixth week follow up as compared to placebo group ($p = 0.008$ & 0.003 respectively). This suggests that vitamin C is helpful in reducing post-operative mid-term pain.

The amount of analgesia consumed by the patients taking vitamin C was significantly lower than that consumed by patients taking placebo ($p = 0.002$), suggesting that vitamin C is helpful in reducing analgesia requirements post-operatively.

Soft tissue trauma associated with a fracture, injury or surgery is one of the major determinants of functional outcome. Vitamin C limits the soft tissue injury by reducing the progression of vascular permeability and hence reducing the leakage of proteins and fluids and also by reducing the lipid peroxidation [25–28]. This may potentially reduce the post-operative swelling. Vitamin C promotes healing of soft tissue and bone by synthesis of intercellular substances like collagen, bone matrix and intercellular cement of the capillary endothelium. In our study, the functional outcome scores of the group which received vitamin C were significantly better than the placebo group ($p \leq 0.001$). It is quite possible that vitamin C supplementation might have limited tissue injury and promoted healing in this group.

There was a high tolerance of vitamin C at the dose administered with no patient discontinuing the drug or the placebo. Vitamin C is a cheap and readily available drug with a very low side effect profile at the dose administered in the study.

This study was limited by a small patient population and a short follow up. The strength of the present study is that it is a prospective, randomized controlled trial with placebo and double blinding. The results strongly suggest a role for vitamin C supplementation in the peri-operative management of pain in patients undergoing foot and ankle surgery. This may be applicable, in fact, to all trauma surgery but that would require further studies; there have, however, already been clear benefits shown in distal radius fractures [22–24].

5. Conclusion

This study shows a clear advantage for patients who have undergone surgery for foot and ankle trauma, receiving vitamin C post-operatively. This was reflected in reduced analgesic requirements and VAS scores and improved early functional outcome. We recommend the use of vitamin C supplementation in foot and ankle trauma surgery.

Conflict of interest

The authors declare that they have no conflict of interest.

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