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ORIGINAL ARTICLE

The influence of high doses of vitamin C on functional recovery and postoperative pain in patients with trochanteric fracture after intramedullary nailing during a three-month follow-up: a pilot study

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ABSTRACT

Aim To determine the effects of high peri- and postoperative doses of vitamin C administration on severity of pain in postoperative period and functional outcome of the patients with trochanteric fracture treated with intramedullary nailing during a three-month follow-up.

Methods A prospective, randomized, pilot study included 56 patients who were randomly divided into vitamin C (intervention) and control groups. In the intervention group, patients received vitamin C perioperatively by an intravenous route for 2 days, and oral vitamin C for 38 days postoperatively. Baseline characteristics, postoperative metamizole consumption, Visual Analogue Scale (VAS) score, Harris Hip Score (HHS) value, and the prevalence of complications were evaluated in both groups.

Results No significant differences were noted between the groups regarding age, gender, length of hospitalization, and distribution in fracture type. Postoperative metamizole consumption was notably higher in the control group compared to the vitamin C group ($p=0.006$). Postoperative VAS score was higher in the control group ($p<0.05$). No significant differences in HHS values were detected between the groups at 6 and 12 weeks postoperatively ($p=0.655$ and $p=0.755$, respectively). The group variable significantly contributed to VAS score, and age and gender variables significantly contributed to HHS value.

Conclusion A significant reduction of subjective pain levels and lower analgesic consumption was found in patients who received vitamin C, suggesting that it should be considered as an adjuvant agent for analgesia in patients with hip fracture.

Keywords: analgesics, antioxidants, femur

INTRODUCTION

Hip fractures are prevalent medical conditions associated with adverse outcomes which carry high morbidity, mortality, and hospitalization in the geriatric population. Due to increasing life expectancy, it is estimated that the number of hip fractures worldwide would rise up to 6.26 million in the next 25 years (1). The mortality rate after hip fracture is between 20% and 24% during the first year (2). Trochanteric fracture type accounts for around 50% of all hip fractures. Intramedullary nailing, as the treatment of choice, is associated with favourable outcomes including decreased duration of operation, lower amount of intraoperative bleeding, and shorter time needed for mobilization (3). Despite the advancement in development of fixation devices, mortality and functional recovery remain unchanged in the last 25 years (4). In the first year postoperatively, between 40% and 60% of trochanteric fracture patients are unable to walk without aids or the other person's assistance (5), and around one third of these patients are admitted to a nursing home (6). Multimodal management of pain after trochanteric fracture, including peripheral nerve blocks, is crucial to avoid delirium in older patients as well as to reduce time to mobilization, reduce length of hospitalization, and improve functional outcome (7).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are mostly used to decrease postoperative pain in musculoskeletal injuries, however, they are associated with gastrointestinal side effects, possible risk of bleeding and negative impact on the cardiovascular system. Vitamin C or ascorbic acid is a vitamin soluble in water, and it is widely known to scavenge reactive oxygen species (ROS) and down-regulate proinflammatory cytokines (8). It has a wide range of use in orthopaedic surgery. Vitamin C reduces the inflammation of joints, and can be used as adjuvant therapy for osteoarthritis (9). Vitamin C also has antinociceptive action with neuroprotective, and neuromodula-

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tory properties (10). Previous studies demonstrated that its usage can decrease pain postoperatively and prevent Sudeck's syndrome in the surgery of foot and ankle as well as after wrist fractures (11,12). In the latest study of Meccariello L et al. (13), authors reported that ion resonance and bromelain-vitamin C help the reduction of complications in the treatment of bimalleolar ankle fractures. The effects of vitamin C in reducing the prevalence of Sudeck's syndrome as well as the improvement of tendon healing after rotator cuff repairs was demonstrated in shoulder surgery (14,15). Behrend H et al. (16) reported that perioperative taking of oral vitamin C prevents its plasma depletion in patients undergoing total knee arthroplasty, and may lower the prevalence of arthrofibrosis, thus improving the range of motion.

Requirement for vitamin C in surgical patients is increased since vitamin C plasma concentration falls after surgery, and further decreases in postoperative period because of oxidative stress (17). Few studies have investigated nutritional status in trauma patients. Vitamins C and D, along with other micronutrients, are deficient in older hospitalized patients (18). Additionally, inadequate vitamin C levels in patients with proximal femur fracture at discharge were associated with increased prevalence of complications in a postoperative period (19). The role of vitamin C was investigated in ankle and foot, distal radius, shoulder and knee surgery (11–16). However, the effects of vitamin C supplementation on postoperative pain and functional recovery after hip fracture surgery were not investigated.

The aim of this pilot study was to determine the effects of peri- and postoperative high doses of vitamin C on severity of postoperative pain and functional outcome of the patients with trochanteric fracture treated with intramedullary nailing during a three-month follow-up.

PATIENTS AND METHODS

Patients and study design

A prospective, randomized, pilot study including 56 patients treated operatively between July 2023 and April 2024 at the Department of Orthopaedics and Traumatology at the Cantonal Hospital Zenica, Bosnia and Herzegovina, was conducted. The patients were randomly divided into vitamin C and control groups using a random number generator (20), with each group consisting of 28 patients.

The inclusion criteria were: trochanteric fracture group including types 31.A1, A2, A3 according to the Arbeitsgemeinschaft für Osteosynthesefragen (AO) classification (21), patients accepting to take part in the study, injury less than two weeks old, patients older than 18 years. The exclusion criteria were: previous surgeries on the extremities, polytrauma, associated injuries, diabetic patients, patients with previous limb amputations, renal insufficiency, cardiorespiratory decompensated patients, coagulation disorders, patients with malignancy, pathologic fractures, any contraindication to surgery, allergies to the medications used in the study, neurological deficit, and patients declining to take part in the study. Baseline characteristics were noted for each patient.

The study was approved by the Ethical Committee of the Cantonal Hospital Zenica (No. 00-03-35-958-10/23). All patients signed a written informed consent.

Methods

The American Society of Anesthesiology Scale was used in the preoperative assessment of patients (22), and all the operations were performed under general anaesthesia. The patients received cefazolin for antibiotic prophylaxis, and dalteparin-sodium subcutaneously for thromboprophylaxis. A short cephalomedullary nail was used for osteosynthesis. Metamizole was used as an analgesic administered intravenously in a maximum daily dose of 5 grams. Patients in the vitamin C group received 2 grams of ascorbic acid in 500 mL saline intravenously half an hour before the incision and 1 gram of ascorbic acid in 500 mL saline intravenously for two days postoperatively. From the 3rd till the 40th postoperative day 1 gram of oral vitamin C was administered daily divided into two doses. The control group of patients did not receive ascorbic acid in any form.

The consumption of parenteral analgesics (metamizole) during postoperative hospitalization was determined. Visual Analogue Scale (VAS) was used to measure subjective pain intensity, Harris Hip Score (HHS) was used to assess functional outcome, and the prevalence of medical and surgical complications in both groups was determined.

The VAS consists of a 10 cm pointed line, with two end points representing 0 as “no pain”, and 10 as ”worst pain possible” (23); it was evaluated at 2 and 14 days, at 6 and 12 weeks postoperatively.

The HHS consists of 4 variables: patient/clinician report of pain, function, deformity, and range of motion (24); it was evaluated at 6 and 12 weeks postoperatively.

Compliance was checked through medication log sheets during postoperative consultations. After discharge, all patients attended the same rehabilitation protocol.

Statistical analysis

Descriptive statistics was used to evaluate baseline characteristics. Variables with normal distribution were presented as median with interquartile range, and those without normal distribution were expressed as mean ± standard deviation (SD). The χ^2 test or Fisher's exact test were used to analyse categorical variables. Continuous variables were analysed either with two-sided Student t- test or Mann-U-Whitney test depending on normality of their distribution. The regression model was used to analyse the contribution of independent variables on dependent variables. In the regression model, age, gender, fracture type, and group were set as independent variables to analyse their contribution on dependent variables (analgesic consumption, VAS score and HHS value). Because of the small sample size, adjusted R^2 values were used to explain variance. Results were considered significant with $p<0.05$.

RESULTS

Out of 56 patients who were included in the study, 39 (69.64%) were females and 17 (30.35%) males (p=0.383). Patients in the vitamin C group were older 79.68 (±6.59) than patients in the control group 78.36 (±8.93), without significance (p=0.532) (Table 1).

Patients in both groups had similar time from admission to surgical intervention (p=0.980). Postoperative duration of hospitalization was without statistically significant difference

Table 1. Baseline characteristics of patients, metamizole consumption, Visual Analogue Scale (VAS) score, and Harris Hip Score (HHS) values across groups

Variables	**Vitamin C group patients** (N=28)	**Control group patients** (N=28)	**p**
Gender (No; %)			
Males	10 (17.86)	7 (12.50)	0.383
Females	18 (32.14)	21 (37.50)	
Age (mean ±SD) (years)	79.68 (±6.59)	78.36 (±8.93)	0.532
Preoperative hospitalization (range) (days)	7 (4-10)	7 (4.5-9.5)	0.980
Postoperative hospitalization (range) (days)	6 (3-9)	7 (4-10)	0.369
Side of fracture (No; %)			
Left	14 (25.00)	16 (28.57)	0.592
Right	14 (25.00)	12 (1.42)	
Fracture type (AO/OTA) (No; %)			
A1	7 (12.50)	6 (10.70)	
A2	19 (33.93)	21 (37.50)	0.775
A3	2 (3.57)	1 (1.78)	
Metamizole consumption (range) (mg)	2500 (1406.25-3593.75)	5000 (3906.75-6093.75)	0.006
Median VAS score (range)			
2 days	5 (4.50-5.50)	6 (4.35-7.37)	0.000
14 days	3 (2.00-4.00)	4 (3.12-4.87)	0.000
6 weeks	2 (2.00-2.00)	3 (2.12-3.87)	0.001
12 weeks	1 (0.62-1.37)	2 (1.50-2.50)	0.11
HHS value (mean±SD**)**			
6 weeks	57.89 (±10.86)	56.43 (±13.29)	0.655
12 weeks	70.66 (±11.76)	71.72 (±13.55)	0.755
Compliance*	**Predicted**	**Consumed**	
Vitamin C 500 mg tablets (No)	2128	1725	

* Compliance is 81%
AO, Arbeitsgemeinschaft für Osteosynthesefragen

between the groups (p=0.369). No significant difference was found in fracture side distribution across the groups (p=0.592). Fracture type distribution across the groups, according to the AO classification, was also not significantly different (p=0.775) (Table 1). The median postoperative metamizole consumption was notably higher in the control group than in the vitamin C group (p=0.006). The median VAS score was higher in the control group compared to the vitamin C group at 2 and 14 postoperative days as well as at 6 and 12 weeks after the operation. The difference between the median VAS score values significantly varied at every follow-up (p<0.05) (Table 1).

The mean HHS value was higher (but not significant) in the vitamin C group (57.89±10.86) compared to the control group (56.43 ± 13.29) at 6 weeks postoperatively (p=0.655). In contrast, the mean HHS value was higher in the control group (71.72 ± 13.55) than in the vitamin C group (70.66 ± 11.76) (but not significant) at 12 weeks postoperatively (p=0.755). Compliance was 81% (Table 1).

One patient in the control group had a superficial wound infection, and one patient in each group had cut out as the surgical complications (Table 2). No postoperative urinary tract infections (UTI) were noticed in the vitamin C group; UTI was found in three female patients of the control group (p=0.118). Postoperative delirium was noted in one patient in the control group, and one patient in the control group had deep vein thrombosis (DVT).

A moderate correlation between the independent variables and analgesic consumption was found (R=0.443), and 19.6% of explained variance. Statistical significance was proved by ANOVA test (p=0.023). The analysis showed that the group variable significantly contributed to analgesic consumption (p=0.009) (Table 3).

The VAS scores showed moderate correlation between the variables at 2 (R=0.560) and 14 days (R=0.641) postoperatively

Table 2. Surgical and medical complications across groups

Surgical complication	**No of patients**		**p**
	Vitamin C group	**Control group**	
Superficial wound infection	0	1	0.500
Cut out	1	1	0.245
Medical complications			
UTI	0	3	0.118
Postoperative delirium	0	1	0.500
DVT	0	1	0.500

UTI, Urinary tract infection; DVT, Deep Vein Thrombosis

Table 3. Contribution of variables to postoperative metamizole consumption*

Metamizole consumption	**Beta**	**t**	**p**
(Constant)		2.925	0.005
Age	-0.217	-1.613	0.113
Gender	0.109	0.836	0.407
Fracture type	0.131	0.968	0.338
Group	-0.345	-2.715	0.009

*Contribution of four independent variables (age, gender, fracture type, and group) to postoperative metamizole consumption;
Beta, standardized coefficient; t, t-test or t value greater than +2 or less than -2 is considered to be statistically significant

with 36.5% and 18.5% of explained variance, respectively, as well as moderate correlation at 6 weeks (R=0.494) and 12 weeks (R=0.457) with 18.5% and 14.7% of explained variance, respectively. The model was confirmed with ANOVA test which was statistically significant for every follow-up time. The analysis showed that the group variable significantly contributed to VAS score at each follow-up point (Table 4).

The HHS values showed a moderate correlation between the variables at 6 weeks (R=0.584) and 12 weeks (R=0.642) postoperatively with 19.6% and 28.9% of the explained vari-

ance. ANOVA test was significant for both follow-up times ($p<0.0005$) (Table 5).

The age and gender were variables that significantly contributed to HHS value at 6 weeks postoperatively ($p<0.0005$ and $p=0.003$, respectively). The same variables significantly contributed to HHS values at 12 weeks postoperatively (Table 5).

Side effects of vitamin C were not noted in this study.

Table 4. Contribution of variables to Visual Analogue Scale (VAS)* score

Model	Beta	t	P
VAS 2 days			
(Constant)		5.130	0.000
Age	-0.024	-0.189	0.851
Gender	0.221	1.831	0.073
Fracture type	-0.159	-1.271	0.210
Group	-0.477	-4.064	0.000
VAS 14 days			
(Constant)		5.130	0.000
Age	-0.024	-0.189	0.851
Gender	0.221	1.831	0.073
Fracture type	-0.159	-1.271	0.210
Group	-0.477	-4.064	0.000
VAS 6 weeks			
(Constant)		4.082	0.000
Age	0.042	0.319	0.751
Gender	0.127	1.001	0.321
Fracture type	-0.207	-1.576	0.121
Group	-0.435	-3.527	0.001
VAS 12 weeks			
(Constant)		3.529	0.001
Age	-0.016	-0.118	0.907
Gender	0.240	1.850	0.070
Fracture type	-0.248	-1.848	0.070
Group	-0.311	-2.469	0.017

*Contribution of four independent variables (age, gender, fracture type, and group) to postoperative VAS score values; Beta, standardized coefficient; t, t-test or t value greater than +2 or less than -2 is considered to be statistically significant

Table 5. Contribution of variables to Harris Hip Score (HHS)* value

Model	Beta	t	P
HHS 6 weeks			
(Constant)		5.005	0.000
Age	-0.367	-3.005	0.004
Gender	-0.430	-3.632	0.001
Fracture type	0.116	0.946	0.349
Group	0.042	0.366	0.716
HHS 12 weeks			
(Constant)		7.433	0.000
Age	-0.490	-4.252	0.000
Gender	-0.352	-3.145	0.003
Fracture type	0.035	0.300	0.765
Group	-0.042	-0.384	0.702

*Contribution of four independent variables (age, gender, fracture type, and group) to postoperative HHS score values; Beta, standardized coefficient; t, t-test or t value greater than +2 or less than -2 is considered to be statistically significant

DISCUSSION

Trochanteric fractures are mostly sustained by patients >70 years of age, with prevalence higher in females (25). Our study population was close to 80 years old, with predomination of females, which shows that demographics of our population are similar to previously reported results (26).

In a study of Jain SK et al. (27), higher VAS scores were reported at 2 and 6 weeks postoperatively in patients who were taking vitamin C after foot and ankle surgery, in comparison to the control; additionally, less analgesic consumption was noted at the end of the 6th week, and functional outcome improved at the end of the third month in patients who were taking vitamin C. Unlike this study, we found significantly lower VAS scores in the vitamin C group at 2 and 6 weeks postoperatively, and functional outcome was not significantly different between the groups at 3 a month follow-up. Lower analgesic consumption in the vitamin C group in our study was found similar with other reports (27). Diabetic patients were not included in our study, and it is probably the reason for a different result compared to a study with an inclusion of diabetics (27).

A meta-analysis (10), which investigated the influence of vitamin C on analgesic consumption in abdominal and gynaecology surgical patients, showed a significantly lower pain score and morphine consumption at postoperative 24 hours. In our study, analgesic consumption also showed significant reduction in patients who received vitamin C with significantly

lower VAS scores at 48 hours postoperatively. Highest pain was expected on the second postoperative day, since drains were removed 48 hours after surgery, patients were taken to control X-ray, and were mobilized on the same day, thus evaluating VAS score at 48 hours postoperatively was important. In contrast, no studies with orthopaedic surgical patients were included in the meta-analysis (10).

A systematic review of factors influencing mortality and functional recovery in trochanteric fracture patients found contradictory results for gender as a contributor to functional outcome; additionally, older age contributes to a lower functional outcome, impairment, and prolonged hospitalization (2). Our results also showed that age significantly affected functional outcome.

Migration of the cephalic screw was noted in one patient in both groups of our study, which is primary surgical complication. Surgical technique is very important in avoiding this complication. Adequate tip-to-apex distance (TAD), anatomic reduction before reaming and passing of the intramedullary nail is mandatory (28). The study of Lanzetti RM et al. (29) showed that with proper surgical technique in stable trochanteric fractures, distal locking is not necessary.

Three female patients in the control group of our study had urinary tract infection (UTI) after surgery. An increased risk for UTI after surgery for trochanteric fracture compared with the risk in patients without it was reported (30). Vitamin C is often recommended as a supplement that can prevent recurrent UTI by acidification of the urine (31).

One of our patients had postoperative superficial wound infection. Despite the possible influence of vitamin C on reducing systemic infections, its potential to increase type 1 collagen synthesis could lead to less local wound healing complications (32).

There were no detected side effects associated with vitamin C in our study, thus vitamin C is a safe, available, and affordable agent.

Considering pharmacokinetics of vitamin C, it is safe to propose oral and intravenous doses of vitamin C of 2 grams daily (33,34).

Since previous studies demonstrated the positive effects of vitamin C in surgery of the joints other than hip fracture one, this study highlights possible analgesic role of vitamin C in hip fracture surgery.

Non-blinding is a limitation of this study. Blinding is difficult because of the different routes of vitamin C administration. Since non-blinding could affect patient reported outcome, objective analgesic consumption was also included in the study as an outcome for more objective pain measurement. We also avoided a placebo effect by not giving a placebo medication.

In conclusion, our findings showed significant reduction of subjective pain levels and lower analgesic consumption in patients who received vitamin C, suggesting that it should be considered as an adjuvant agent for analgesia in patients with hip fracture. Age and gender predominantly affected the functional outcome.

A full-scale study is needed to generalize the results, further evaluate their significance and clinical outcomes.

AUTHOR CONTRIBUTIONS

Conceptualization, M.S. and Đ.O.; methodology, M.S., F.L. and A.P.; software, M.S. and F.L.; validation, M.S., Đ.O. and F.L.; formal analysis, M.S.; investigation, M.S. and F.L.; resources, Đ.O.; data curation, A.P.; writing—original draft preparation, M.S. and Đ.O.; writing—review and editing, M.S.; visualization, Đ.O.; supervision, Đ.O.; project administration, A.P. All authors have read and agreed to the published version of the manuscript.

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Conflict of interests: None to declare.

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