JEMTAC
Journal of Emergency Medicine Trauma & Acute Care
A PEER REVIEWED JOURNAL

OPEN ACCESS

Research Paper

Effect of vitamin C on postoperative pain in patients undergoing lower limb surgery

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https://doi.org/10.5339/jemtac.2025.36

Submitted: 26 February 2025
Accepted: 03 June 2025
Published: 18 September 2025

ABSTRACT

Introduction: Effective reduction of post-operative pain is vital for patient care, early mobilization, quick recovery, and a brief hospital stay. Vitamin C has been explored for its potential analgesic properties in postoperative settings, but its clinical utility remains inconclusive. Our study aimed to assess the effect of vitamin C on post-operative pain in patients undergoing lower limb surgery and its safety profile.

Methods: This randomized, open-label, parallel-group study investigated the effectiveness of vitamin C supplementation as an additional treatment alongside standard pain management in patients undergoing lower limb orthopaedic surgery. The study was conducted by the Departments of Pharmacology and Orthopaedics. Participants were randomly divided into two groups. One group received vitamin C 500 mg orally twice daily for 5 consecutive days postoperatively, with the first dose administered 6 hours after surgery, while the other group was the control. Both groups received diclofenac 50 mg intramuscularly twice daily. Pain levels were measured using the Visual Analogue Scale (VAS) and the Behavioural Pain Assessment Scale (BPAS) at different time intervals. The unpaired *t*-test was applied to compare the pain scores between the two groups.

Results: A total of 100 patients were recruited, with 50 in each group. Demographic parameters were comparable. Mean age was 41.98 ± 14.91 and 38.1 ± 13.87 years in the vitamin C and control groups, respectively, with 80% men in both groups. Pain intensity was comparable, and all patients had severe limitation of joint movements in both groups at baseline. Reduction in VAS and BPAS score was significant ($p < 0.05$) with vitamin C. No adverse effects were reported with vitamin C.

Conclusion: Vitamin C supplementation significantly improved pain management outcomes postoperatively, suggesting its potential as an adjunct to traditional analgesics for patients undergoing lower limb orthopaedic surgery.

Keywords: Vitamin C, post-operative pain, lower limb surgery, Visual Analogue Scale, Behavioural Pain Assessment Score, Functional Activity Score

1. INTRODUCTION

Pain is the most common problem encountered in the immediate postoperative period. Effective control of this postoperative pain is vital for improved patient care, early mobilization, faster

Cite this article as: Sarathy MP, Krishnaswamy B, Shanthappa AH. Effect of vitamin C on postoperative pain in patients undergoing lower limb surgery. *Journal of Emergency Medicine, Trauma & Acute Care*. 2025(3):36 https://doi.org/10.5339/jemtac.2025.36

recovery, and shorter hospital stay, especially in patients undergoing orthopedic surgeries.[1] Side effects associated with the use of analgesics like opioids and non-steroidal anti-inflammatory drugs (NSAIDs) may result in inadequate pain relief in the post-operative period in 75% of individuals.[2] Hence, multimodal analgesia is being tried to relieve pain completely, and studies are needed in this regard.

Vitamin C (ascorbic acid) is known to be beneficial for patients with the common cold, in wound healing, infertility, and Alzheimer's disease.[3] Vitamin C is present throughout the body, but a higher concentration is observed in the brain.[4] It may cause analgesia due to its potent antioxidant effect, and this action may help to protect the tissues by scavenging the reactive oxygen species generated during oxidative damage that occurs during surgery. Low plasma levels of ascorbic acid were observed following an injury, suggestive of consumption of large quantities of vitamin C from the reserve.[5]

Depletion of vitamin C during acute/chronic disease or trauma may be responsible for the pain symptoms. The basis for this could be reduced synthesis of neurotransmitters (norepinephrine, dopamine, serotonin) with analgesic activity, and their levels may increase with supplementation of vitamin C.[5] They regulate the glutamate receptor binding on the NMDA receptors, which is responsible for the windup phenomenon of pain.[6] It may also exhibit analgesia by increasing the synthesis of endorphins.[5] Thus, vitamin C can be used as a component of multimodal analgesia.[6] Vitamin C supplementation has shown analgesic effects in hip and knee osteoarthritis patients, reduced the dose of morphine post-operatively after laparoscopic cholecystectomy, and incidence of chronic regional pain syndrome in patients after wrist, ankle, and foot surgery.[7–9] Vitamin C supplementation in the range of 0.5 to 3 g/day is effective in reducing pain, which may be attributed to multiple actions of vitamin C, but the exact site and mechanism of action of vitamin C for postoperative pain relief are not yet fully understood.[4,7]

Even though studies have shown the beneficial effect of vitamin C in the management of pain without significant side effects,[2,7,10] there are few studies in India evaluating the role of vitamin C as an adjunct to analgesic medications for pain relief following orthopaedic procedures performed for fracture of bone. Hence, this was carried out to assess the effect of vitamin C on post-operative pain in patients undergoing lower limb surgery and its safety profile.

2. MATERIALS AND METHODS

This study was conducted by the Departments of Pharmacology and Orthopaedics at a tertiary care medical college hospital in India, from January 2021 to July 2022. The participants included both male and female patients, aged 18 to 65 years, who were undergoing lower limb orthopaedic surgery under spinal anesthesia. Only those classified as American Society of Anesthesiologists (ASA) grade I and II were included in the study. Patients with hepatic or renal impairment, renal calculi, hemorrhagic disorders, bronchial asthma, peripheral neuropathy, addictive disorders (including smoking, alcoholism, and drug abuse), a history of peptic ulcer or gastrointestinal bleeding, and pregnant or lactating women were excluded from the study.

The patient details were collected according to the protocol designed for the study. A total of 108 patients were screened for eligibility, and eight patients were excluded based on the predefined eligibility criteria. After the screening process, 100 patients were randomly allocated into two groups: Group CTRL (control) and Group V (vitamin C). The allocation was performed using computer-generated random numbers, ensuring that each patient had an equal chance of being assigned to either group. The computer-generated randomization sequence was used to assign patients to the groups in a 1:1 ratio. The study was designed as an open-label, parallel-group, comparative trial, meaning that both the patients and healthcare providers were aware of the assigned treatment groups. The following investigations were done preoperatively: Complete hemogram, urine routine, blood urea, serum creatinine, bleeding time, clotting time, fasting blood sugar, and tests for HIV and HBsAg.

Patients of both groups who underwent lower limb orthopedic surgery under spinal anesthesia received an injection of diclofenac 50 mg intramuscularly twice daily for 5 days (morning and night) in the immediate postoperative period. However, in instances where patients experienced insufficient pain relief, additional analgesics such as paracetamol and opioids were given as rescue medication. Six hours after surgery and from day 1 to day 5 of the postoperative period, patients in group V received 500 mg of vitamin C orally, twice daily, administered 30 minutes before meals. The supplementation began on the day of surgery and continued for 5 days postoperatively. The oral

Table 1. Behavioural Pain Assessment Scale (BPAS).

Categories	Scoring			Total score
	Score 0	Score 1	Score 2	
Face	Face muscles relaxed	Face muscle tension, grimace, grown	Frequent to constant frown, clenched jaw	
Restlessness	Quiet, Relaxed appearance, normal movement	Occasional restless movement, shifting position	Frequent restless movement may include the extremities or the head	
Muscle tone	Normal muscle tone	Increased tone, flexion of fingers and toes	Rigid tone	
Vocalization	No abnormal sounds	Occasional moans, cries, whimpers, and grunts	Frequent or continuous moans, cries, whimpers, or grunts	
Consolability	Content, relaxed	Reassured by touch, distractible	Difficult to comfort by touch or talk	
Behaviour Pain Assessment Scale total (0–10)				

Note: Observe behavior and rate each of the five measurement categories (0, 1, or 2) according to the description provided, then add these ratings together and document the total pain score out of 10.

Table 2. Functional Activity Score (FAS).

Score	Limitation	Yes/no
A	No limitation (perform task without pain)	
B	Mild limitation (perform task with minimal pain)	
C	Severe limitation (unable to perform the task)	

Note: Functional activity scoring was done after the return of motor function. Patients were observed during the chosen activity/task (move the affected leg—i.e., toes, ankle) and scored as A, B, and C.

route was selected for its convenience, patient adherence, and reliable absorption at moderate doses. This specific dosing protocol was based on previous studies suggesting vitamin C's potential role in managing postoperative pain, while ensuring it remained within the recommended and well-tolerated daily intake range. Patients were educated about the pain scoring system and were requested to report any adverse events encountered during their hospital stay. The patient's pulse rate (PR), blood pressure, and respiratory rate (RR) were monitored immediately after recovery from anesthesia, which is four hours postoperatively, and also at 120 hours postoperatively.

The intensity of pain was measured using the Visual Analogue Scale (VAS) score from 0 to 10 (0 = no pain and 10 = worst pain). VAS score is classified as no pain = 0, mild = 1 to 3, moderate = 4 to 7, severe = 8 to 10. VAS score was measured at baseline (before study medication was administered) and at 2, 4, 8, 12, 24, 48, 72, 96, and 120 hours. Total pain relief (TOTPAR) was calculated by multiplying the current pain relief (pain intensity difference) at each time point by the duration (in hours) since the preceding time point and then summing those over the relevant time period (12, 24, 48, 72, 96, and 120 hours). Objective pain scales like the Behavioural Pain Assessment Scale (BPAS) and Functional Activity Score (FAS), described in Tables 1 and 2, were evaluated at baseline and at 12, 24, 48, 72, 96, and 120 hours. Patient satisfaction with pain relief was assessed using a Patient Satisfaction Score (PSS) on a scale of 1 = poor, 2 = fair, 3 = good, 4 = excellent at the end of 24, 72, and 120 hours postoperatively. Adverse events, if any, to vitamin C and diclofenac were monitored using the WHO causality scale.[11]

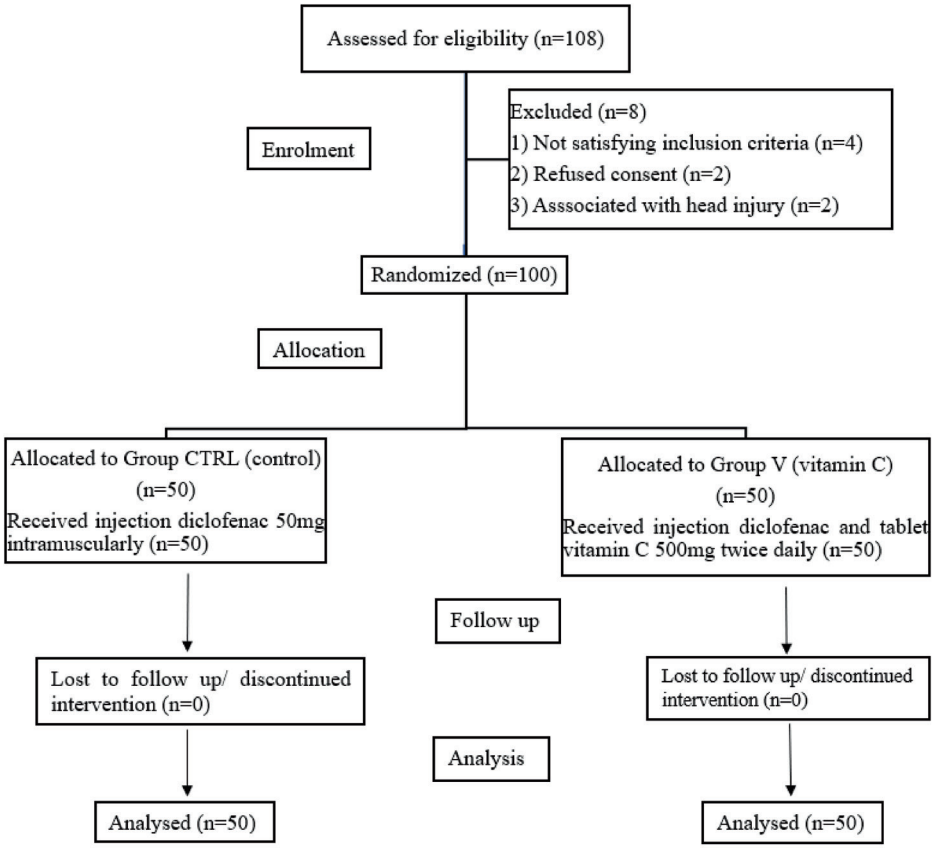

Figure 1. CONSORT flow chart representing recruitment of patients.

2.1 Statistical Tests

The sample size was calculated based on a power of 90% and an alpha error of 5% to detect a mean difference of 0.8 in the total VAS score, with an effect size of 0.88 and accounting for a 20% dropout rate. This calculation was based on the study on postoperative pain management by Chinnaiyan *et al*, which involved a comparable patient population and intervention setting. Based on this reference, a sample size of 34 patients per group was found to provide adequate statistical power.[1] The demographic data were analyzed using descriptive statistics. The VAS and BPAS scores were analyzed by repeated measures ANOVA within the groups and unpaired *t*-test between the groups at each interval. Graded VAS score and Functional Activity Score between groups were analyzed using Mann Mann-Whitney *U* test. Adverse effects (if any) were analyzed by the chi-square test. A *p*-value less than 0.05 was considered to be statistically significant.

2.2 Ethical consideration

In this study, no interventions were conducted outside the designated areas, and no additional costs were incurred for the inclusion of participants. Patients had the option to withdraw from the study at any point. All participants provided written informed consent. The study protocol received approval from the Institutional Ethics Committee of Tertiary Medical College.

3. RESULTS

A total of 100 patients undergoing lower limb orthopedic surgery under spinal anesthesia were included in the study to assess the effect of Vitamin-C on post-operative pain relief and to evaluate its safety profile. They were randomized into control (CTRL) and vitamin C (V) groups with 50 patients in each group. All the patients completed the study (Figure 1—CONSORT diagram).

Table 3. Comparison of baseline characteristics of patients between groups.

Variables	Control (*n* = 50)	Vitamin C (*n* = 50)	*p* value
Age (years)	41.98 ± 14.91	38.10 ± 13.87	0.09
Male/female	40/10	40/10	
Duration of surgery (minutes)	105 ± 35.99	105 ± 35.99	0.30

Note: Values are expressed as mean ± SD. Unpaired *t*-test.

Table 4. Type of lower limb fractures.

Type of fracture	Control (*n* = 50)	Vitamin C (*n* = 50)
Tibial fracture	12	9
Femur shaft fracture	8	8
Both tibia and fibula fractures	7	6
Femur intertrochanteric fracture	6	8
Isolated medial malleolar fracture	5	2
Bi malleolar fracture	2	2
Femur with implant	2	3
Tibia with an implant	1	3
Isolated fibula fracture	1	0
Patella fracture	0	2
Others	6	7

In our study, out of 100, 80 were male and 20 were female patients, but the gender distribution was equal in both groups. The demographic variables like age, gender, and mean duration of the surgery were comparable between the groups (Table 3).

Systolic blood pressure (SBP), diastolic blood pressure (DBP), PR, and RR were recorded postoperatively at 4 hours (baseline) and on day 5. SBP was reduced significantly on day 5 compared to baseline in the vitamin C group and DBP in the control group. There were no statistically significant differences between the two groups at either time point. All the vital parameters were within the normal range in both groups.

In the control group, 41 patients and 37 in the vitamin C group who had a fracture in the lower limb had undergone closed reduction and internal fixation (CRIF). Three and six patients in the control and vitamin C groups had implants in situ, and they underwent implant removal. Six and seven patients in the control and vitamin C groups had undergone procedures such as meniscal repair, wound debridement, and arthrotomy (Table 4).

The VAS score was comparable between the groups immediately following surgery (0 hours). The VAS score reduced significantly in both control and vitamin C groups at 120 hours compared to 0 hours. This reduction was observed in 4 hours itself. The reduction in VAS score from 4 hours post-operatively till 120 hours (day 5) in the vitamin C group was statistically significant compared to the control, although it was not so at 24 and 48 hours (Table 5).

The percentage of patients with severe pain was 72% versus 56% in the control versus the vitamin C at 2 hours, and moderate pain was observed in 90% versus 96%, 96% versus 94% at 12 hours and 24 hours, respectively. The progression of postoperative pain intensity over time demonstrated a more favorable trend in the vitamin C group compared to the control group. While both groups initially reported high levels of moderate to severe pain, patients receiving vitamin C experienced a more rapid shift toward lower pain levels. These findings suggest that oral vitamin C supplementation may contribute to a faster and more effective reduction in postoperative pain intensity (Table 6).

Table 5. Visual Analogue Scale score in patients within and between groups.

Time (hours)	Control (n = 50) mean ± SD)	Vitamin C (n = 50) (mean ± SD)	p value
0	8.34 ± 0.79	8.30 ± 0.76	0.79
2	7.88 ± 0.93	7.66 ± 0.87	0.22
4	7.34 ± 1.02	6.86 ± 0.85	0.01*
8	6.68 ± 1.20	6.24 ± 0.98	0.04*
12	6.16 ± 1.11	5.54 ± 1.07	0.006*
24	5.40 ± 1.06	5.02 ± 1.05	0.07
48	4.66 ± 1.15	4.26 ± 0.94	0.06
72	3.98 ± 0.86	3.42 ± 0.94	0.003*
96	3.40 ± 0.88	2.78 ± 0.86	0.001*
120	2.84 ± 0.88	2.20 ± 0.67	0.001*
p value	0.0001#	0.0001#	

Note: R-ANOVA within group and unpaired "t" test between the groups.
#p within group; *p between groups.

Table 6. Graded VAS score between groups at different time intervals.

Time (hours)	Control (n = 50)			Vitamin C (n = 50)		
	Mild (1–3)	Moderate (4–7)	Severe (8–10)	Mild (1–3)	Moderate (4–7)	Severe (8–10)
2	0	14	36	0	22	28
4	0	25	25	0	41	9
8	0	36	14	0	45	5
12	0	45	5	0	48	2
24	2	48	0	3	47	0
48	6	44	0	10	40	0
72	12	38	0	28	22	0
96	23	27	0	43	7	0
120	39	11	0	49	1	0

TOTPAR was calculated as the sum of the patient responses to pain relief over 12, 24, 48, 72, 96, and 120 hours. TOTPAR at 12 (32.16 vs. 22.92), 24, 48, 72, 96, and 120 (741.6 vs. 667.2) hours was higher in the vitamin C group compared to the control group (Figure 2).

The BPAS score was comparable between the groups at baseline (0 hours). There was a significant reduction in BPAS score from 12 hours following surgery till 120 hours compared to baseline in both the treatment groups. The reduction in BPAS score was statistically significant with vitamin C compared to control from 12 hours itself (Table 7).

There was a severe limitation of movements in all patients in both groups at 0 hours postoperatively. At 72 hours, 54% of patients in the vitamin C group had no limitation to movements, which was increased to 90% patients at 120 hours, but in the control group, it was 28% (72 hours) and 82% (120 hours; Table 8).

At 24 hours and 72 hours satisfaction score was expressed as good in control vs vitamin C (12% vs. 38%) and (52% vs. 60%), respectively, but at 120 hours satisfaction score was excellent in 24% vs 50%. One patient in the vitamin C group reported bloating on the second postoperative day, and later it subsided (Figure 3).

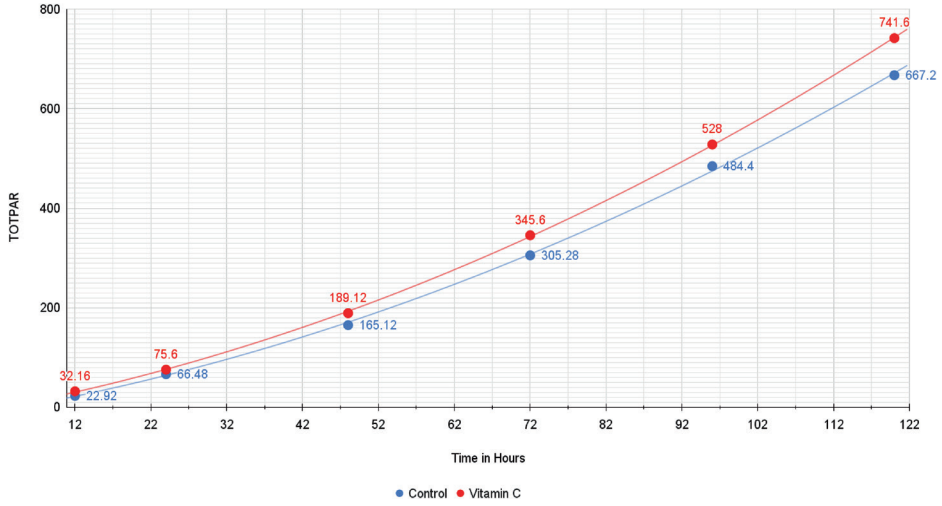

Figure 2. Total pain relief (TOTPAR) in both groups.

Table 7. Behavioral Pain Assessment Scale (BPAS) score within and between groups.

Time (hours)	Control (n = 50) (Mean ± SD)	Vitamin C (n = 50) (Mean ± SD)	*p* value
0	8.34 ± 0.79	8.34 ± 0.82	1.0
12	6.62 ± 1.06	5.68 ± 0.97	0.0001*
24	5.64 ± 1.06	4.92 ± 0.98	0.001*
48	4.82 ± 1.04	4.00 ± 1.03	0.0001*
72	4.06 ± 0.93	3.38 ± 0.83	0.0001*
96	3.46 ± 0.88	2.58 ± 0.75	0.0001*
120	2.88 ± 0.87	2.16 ± 0.61	0.0001*
p value	0.0001#	0.0001#	

Note: R-ANOVA, #*p* within group. Unpaired "*t*" test, **p* between groups.

Table 8. Functional Activity Score between groups.

Time (hours)	Patients with limitations in the range of movements						*p* value
	No		Moderate		Severe		
	Control (%)	Vitamin C (%)	Control (%)	Vitamin C (%)	Control (%)	Vitamin C (%)	
0	0	0	0	0	100	100	1.00
12	0	0	28	30	72	70	0.82
24	0	0	68	80	32	20	0.17
48	16	6	78	92	6	2	0.40
72	28	54	62	46	0	0	0.009*
96	64	80	36	20	0	0	0.07
120	82	90	18	10	0	0	0.25

Note: Mann-Whitney *U* test, **p* between groups.

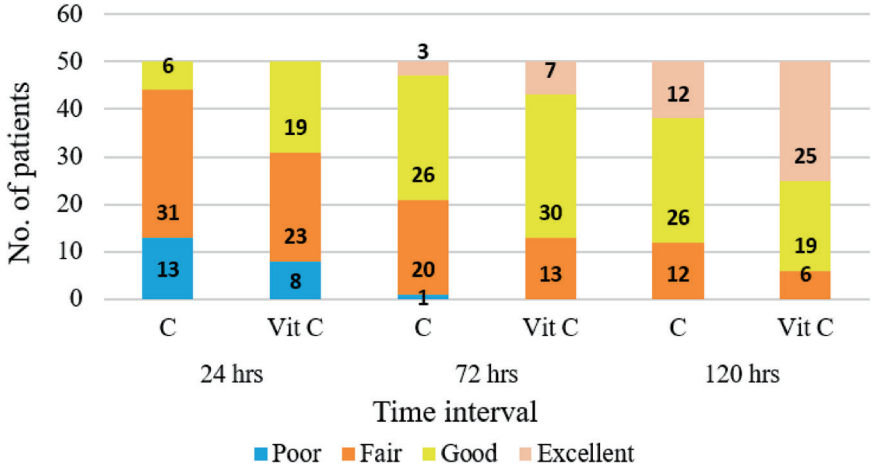

Figure 3. Patient Satisfaction Score between groups.

4. DISCUSSION

Postoperative pain following surgery is a challenge both for the patient and the healthcare professionals. Orthopedic surgeries have the potential to result in severe intraoperative and postoperative pain, which is a sign of tissue damage and typically an important clinical issue. Inadequately controlled postoperative pain may result in longer hospital stay, poor wound healing, an increase in morbidity and mortality, poor quality of life, and patient dissatisfaction. Management of postoperative pain adequately is a challenge due to the side effects encountered with analgesics like opioids or NSAIDS. Therefore, modern clinical practice guidelines recommend a multimodal approach to pain management, including the use of different analgesic drugs and non-pharmacological interventions.[2]

Vitamin C can be used as an adjuvant to analgesics for pain relief, which in turn may help in quick rehabilitation, muscle strength for ambulation, and recovery of range of movements following orthopedic surgery. Vitamin C, also known as L- L-ascorbic acid, has several important functions in the human body. It is a water-soluble vitamin that exerts anti-nociceptive action through its antioxidant property. It plays an important role in the healing of skin and scar tissue, blood vessels, ligaments, and tendons.[4] It limits tissue injury by scavenging the reactive oxygen species, which are formed due to stress during surgery, and has neuroprotective and neuromodulation effects.[12–14] A recent study by Ranjbari *et al* concluded that vitamin C supplementation has emerged as a potential adjunctive therapy for postoperative spinal pain. Its antioxidant properties and role in collagen synthesis suggest the potential for pain relief and improved healing outcomes.[15]

The majority of patients in our study were males, which was similar to other studies.[4] The patients were aged between 25 to 42 years in the vitamin C (V) group, whereas in other studies, it was between 20 and 60 years.[4] SBP increases in response to pain, and in our study, we observed that the reduction was significant in the vitamin C (V) group, which indicates pain relief compared to the control. The mode of injury in the majority of patients in both groups was due to a road traffic accident followed by a fall. Since various bones have varied pain thresholds, only individuals having surgery on their lower limbs were recruited. The proportion of surgical procedures performed in each group was approximately the same, with CRIF surgeries being the most common. The average duration of surgery was comparable in both groups of patients.

The mean VAS score was comparable between the two groups at baseline (Table 5). Pain reduction due to diclofenac was noted in both groups when compared to baseline, but a significant decrease in VAS score was observed in patients receiving vitamin C at 4, 8, 12, 72, 96, and 120 hours after surgery compared to the control group (Table 5). This may be due to vitamin C contributing to pain relief from day 1 to day 5. In a study, the onset of the vitamin C effect was observed 6 hours following its administration.[14]

The majority of patients had moderate intensity of pain in the vitamin C (V) group compared to the control group (CTRL; $p = 0.002$) at 12 hours postoperatively (Table 6). Ninety eight percent of patients in the vitamin C (V) group had mild pain compared to 78% in control group (CTRL; $p = 0.004$)

on day 5, as in Table 6, suggestive of a sustained effect of vitamin C. TOTPAR was higher in the vitamin C (V) group at all time points till day 5 (Figure 2). This may be due to the effect of vitamin C on pain relief.

The findings of a meta-analysis of randomized controlled trials have shown that intravenous supplementation of vitamin C has decreased pain scores at 1 to 2 hours, 6 hours, and 24 hours postoperatively, but when given orally, there was significant pain relief at 6 hours only.[8] Another study has shown that the reduction in pain relief in the vitamin C group was also observed in patients undergoing ankle and foot surgeries at week 2 and 6.[4] Administration of vitamin C 2g orally 2 hours before surgery had produced a significant difference in pain at 30 minutes postoperatively following laparoscopic surgery.[13]

Reduction in BPAS subjective pain score in the vitamin C group (V) was significant at all time points compared to the control (Table 7). This may be indicative of vitamin C augmenting the analgesic action of diclofenac. Fifty-four percent of patients in the vitamin C group had moderate limitation to movement in the postoperative period at 72 hours, probably due to pain, but on day 5, 90% of them had a complete range of movements, indicating no pain on activity (Table 8). In a study by Lee *et al*, tablet vitamin C was given postoperatively from day 1 till 45 days, which improved the functional status of patients following surgery significantly during the first three postoperative months.[16]

A study by Ramon *et al* found that administering 15 g of vitamin C postoperatively reduced inflammatory markers and decreased the need for opioid analgesics, suggesting a potential benefit in managing postoperative pain for patients undergoing total knee arthroplasty.[17] The study by Mirza Sivro and colleagues demonstrated that patients administered high doses of vitamin C experienced significantly reduced postoperative pain, as evidenced by lower VAS scores and decreased consumption of analgesics compared to the control group following lower limb surgery.[18]

The PSS in the vitamin C group (V) was expressed as Fair-good by 42 patients (37 in control) at 24 hours and as Good-excellent on day 5 by 44 patients (38 in control), as shown in Figure 3. This indicates the benefit of vitamin C in providing pain relief. One patient in the vitamin C group had bloating, which subsided with no further complaints. It was observed in another study that there were no serious adverse effects of vitamin C on prolonged administration for a duration of 45 days.[18] This shows that vitamin C could be more effective in relieving pain on prolonged administration and does not cause any serious adverse effects.

5. CONCLUSION

Patients who undergo lower limb orthopedic surgery benefit from taking vitamin C in the postoperative period since it decreases pain and restores the functions of joints without causing any adverse effects. Thus, vitamin C can be used as an adjuvant to diclofenac for the control of pain following lower limb surgeries.

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