Effectiveness of Vitamin C Injection in Preventing Acute Pain Following Laparoscopic Cholecystectomy: A Randomized Clinical Trial

Al-Yassin V. MD[1], Dehghani A. MD[2*]

Abstract:

Background and Objective: Acute pain following laparoscopic cholecystectomy remains a significant clinical challenge that can adversely affect recovery and patient satisfaction. Given the limitations and adverse effects associated with conventional analgesic strategies, there is growing interest in safer adjunctive approaches. Due to its antioxidant and anti-inflammatory properties, vitamin C may represent a promising option in this setting. This study aimed to evaluate the effectiveness of intravenous vitamin C administration in preventing acute postoperative pain after laparoscopic cholecystectomy.

Methods: This randomized, double-blind clinical trial was conducted on 70 eligible volunteer patients scheduled for laparoscopic cholecystectomy. Participants were randomly assigned to either the vitamin C group or the placebo group, with 35 patients in each group. The intervention consisted of intravenous administration of vitamin C. Pain intensity was assessed using the Visual Analog Scale (VAS) during the first 24 hours after surgery. Data were analyzed using independent samples t-tests and chi-square tests. A p-value of less than 0.05 was considered statistically significant.

Results: Post hoc comparisons with Bonferroni adjustment demonstrated significant differences between the two groups at 6, 12, 18, and 24 hours after surgery, indicating a sustained effect of vitamin C in reducing acute postoperative pain. Repeated-measures analysis revealed a significant effect of time on pain intensity ($P < 0.001$, partial $\eta^2 = 0.41$), showing that pain severity decreased over time in both groups. A significant group effect was also observed ($P < 0.001$, partial $\eta^2 = 0.29$), with patients in the vitamin C group experiencing overall lower pain intensity than those in the control group. In addition, the time-by-group interaction was significant ($P < 0.001$, partial $\eta^2 = 0.18$), indicating that the reduction in pain over time was more favorable in the vitamin C group than in the control group.

Conclusion: The findings of this study suggest that intravenous vitamin C administration is an effective and practical intervention for preventing acute pain following laparoscopic cholecystectomy. This approach may contribute to improved clinical outcomes and an enhanced patient experience.

Keywords: Ascorbic Acid; Cholecystectomy, Laparoscopic; Acute Pain

[1] Resident in Cardiothoracic Surgery, School of Medicine, Tehran University of Medical Sciences, Rajaie Hospital

[2] Associate Professor of Anesthesiology, Department of Anesthesiology, School of Medicine, Tabriz University of Medical Sciences, Imam Reza Hospital

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Corresponding Author: Dr. Abbasali Dehghani

Tel: 041-33353639
E-mail: AAdehghani@gmail.com

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Background and Objective

Acute postoperative pain is one of the most common and challenging complications following abdominal surgery. It can directly affect the recovery trajectory, length of hospitalization, patient satisfaction, and the development of secondary complications. Laparoscopic cholecystectomy, considered the standard treatment for benign gallbladder disease, is associated with less surgical trauma and a shorter convalescence period than open surgery. Nevertheless, it is still frequently accompanied by acute postoperative pain, particularly during the first hours and days after the procedure. This pain is multifactorial in origin and may include incisional pain, diaphragmatic irritation, visceral pain, and referred shoulder pain caused by residual CO2 within the abdominal cavity.[1] Despite substantial advances in surgical and anesthetic techniques, effective pain control after laparoscopic cholecystectomy remains a major clinical priority, as inadequately controlled pain can restrict deep breathing, impair early mobilization, and increase the risk of pulmonary complications.[2] Accordingly, the search for safe, effective, and low-risk strategies to prevent and reduce acute pain after this procedure continues to attract considerable research interest.[3]

A variety of approaches have been employed to manage pain following laparoscopic cholecystectomy, including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics, nerve blocks, and adjunctive pharmacologic interventions. Although opioids effectively reduce pain intensity, their use is associated with adverse effects such as nausea, vomiting, constipation, urinary retention, and the potential for dependence.[4] Conversely, NSAIDs and acetaminophen alone may be insufficient for complete pain control and may also be contraindicated or limited in certain patients.[5] In this context, adjunctive agents with distinct mechanisms of action that can reduce pain severity and minimize opioid requirements have gained attention as part of a multimodal analgesic strategy.[6]

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin with potent antioxidant properties that plays an important role in neutralizing free radicals, modulating inflammatory responses, and supporting immune function.[7] Increasing evidence suggests that oxidative stress and the inflammatory response triggered by surgical tissue injury significantly contribute to the development and persistence of acute postoperative pain.[8] In this regard, vitamin C may help alleviate postoperative pain by reducing the production of inflammatory cytokines and inhibiting pathways involved in both peripheral and central sensitization.[9]

Numerous studies have investigated the role of vitamin C in reducing both acute and chronic pain across various clinical settings. Their findings suggest that vitamin C administration may reduce pain intensity, improve functional recovery, and reduce the need for analgesic medications.[10] Specifically, the analgesic effects of vitamin C have been observed in conditions such as postoperative pain following orthopedic procedures, neuropathic pain, and complex regional pain syndrome.[11] Proposed mechanisms include the inhibition of glutamate release, attenuation of NMDA receptor activation, and reduction of neuroinflammation, all of which are key contributors to pain pathophysiology.[12]

In laparoscopic surgery, the role of vitamin C as an adjunctive intervention for postoperative pain control has been less extensively studied; however, available evidence suggests considerable potential in this area. Some studies have shown that perioperative intravenous administration of vitamin C may reduce pain intensity and opioid consumption during the first 24 to 48 hours after surgery.[13] These findings support the hypothesis that vitamin C could serve as a valuable component of multimodal postoperative pain management.[14] Given its favorable safety profile, low cost, and wide availability, evaluating the effectiveness of vitamin C in common procedures such as laparoscopic cholecystectomy is particularly clinically relevant.[15]

Despite these promising findings, evidence regarding the precise effectiveness

of intravenous vitamin C in preventing acute pain after laparoscopic cholecystectomy remains limited, and the results of published studies have been somewhat inconsistent.[16] Differences in dosage, timing of administration, route of delivery, and pain assessment methods may all contribute to variability in study outcomes.[17] Therefore, well-designed clinical trials with appropriate control of confounding variables are needed to provide more robust evidence. Given the high frequency of laparoscopic cholecystectomy, the importance of effective acute postoperative pain control, and the potential role of vitamin C in modulating inflammatory and pain responses, the present study was conducted to determine the effectiveness of intravenous vitamin C administration in preventing acute pain after laparoscopic cholecystectomy.

Materials and Methods

Study Design

This study was designed as a randomized, double-blind clinical trial to evaluate the efficacy of intravenous vitamin C administration in preventing acute pain following laparoscopic cholecystectomy. The study was conducted in 2024 at Imam Reza Hospital, Tabriz University of Medical Sciences. A total of 70 patients scheduled for laparoscopic cholecystectomy were enrolled through convenience sampling from eligible volunteer. Participants were randomly assigned to either the vitamin C group or the placebo group. To ensure procedural consistency, all patients were managed by the same surgical and anesthesia teams throughout the study.

Sample Size

The sample size was calculated using the Pocock formula for comparing the means of two independent groups. In this formula, n denotes the required sample size per group; $1-\alpha/2=1.96$ corresponds to a 95% confidence level; and $1-\beta=0.84$ corresponds to 80% statistical power. The standard deviation of the primary study variable in both groups and the minimum expected difference between group means were also incorporated into the calculation. Based on the findings reported by Alpsoy et al., [4] and after accounting for 80% power, a type I error of 5%, and the possibility of sample attrition, the required sample size was estimated at 35 patients per group. Accordingly, a total of 70 patients were included in the study.

Inclusion and Exclusion Criteria

Eligible participants were adults aged 18 to 65 years who were hospitalized for elective laparoscopic cholecystectomy and classified as American Society of Anesthesiologists (ASA) physical status I or II. Additional inclusion criteria included providing written informed consent, the ability to tolerate general anesthesia, and no use of medications affecting pain pathways or strong antioxidant agents during the week preceding surgery.

Exclusion criteria included unwillingness to continue participation or withdrawal at any stage, allergic reactions or intolerance to the study medication, chronic use of opioids or benzodiazepines, a history of major neurological or psychiatric disorders, severe cardiopulmonary disease, renal or hepatic failure, uncontrolled diabetes mellitus, a history of difficult airway management or tracheal intubation, and known hypersensitivity to lidocaine or vitamin C. Additionally, patients whose surgery lasted longer than three hours or who developed severe complications that precluded complete follow-up were excluded from the study. All eligibility criteria were carefully assessed preoperatively by the attending anesthesiologist and the principal investigator.

Randomization

Randomization was performed using a computer-generated random number table. First, a list of numeric codes from 1 to 70 was prepared for the enrolled patients. Random numbers were then generated in two separate columns using Microsoft Excel. Based on the order of enrollment and matching with the randomization table, patients were allocated to the two study groups in blocks of four. Within each block, two patients were assigned to the intervention group (vitamin C) and two to the control group (placebo), ensuring balanced allocation. Group assignments were placed in opaque, sealed envelopes, and

the allocation codes remained concealed from both the treatment team and the statistical analyst until the completion of the analysis. Since the total sample size was 70, fixed blocks of four alone could not accommodate all participants. Therefore, the allocation sequence was generated randomly using four-patient blocks; after assigning 68 patients within 17 complete blocks, the remaining two patients were allocated by simple randomization to preserve the final balance of 35 participants in each group.

Blinding

The trial was conducted in a double-blind manner, meaning that both the patients and the investigator responsible for data collection were unaware of group allocation. Preparation of the infusion solutions was performed by the ward nurse, who had no role in data collection or outcome assessment. The bottles containing vitamin C (500 mg in 50 mL isotonic normal saline) and the placebo (plain normal saline) were identical in appearance and consistency, differing only in their coded labels. Thus, blinding of both participants and investigators was fully maintained.

Study Procedure

In the vitamin C group, patients received 500 mg of vitamin C diluted in 50 mL of isotonic normal saline, administered as an intravenous infusion over 10 minutes twice daily, from the day of surgery until two days postoperatively. Infusions were administered each day at 7:00 AM and 8:00 PM by the ward nurse. The control group received a placebo consisting of normal saline following the same schedule.

General anesthesia was induced with propofol (2 mg/kg) and lidocaine (1 mg/kg), and tracheal intubation was facilitated with atracurium (0.5 mg/kg). Anesthesia was maintained with isoflurane (1%–2%) in a 50% oxygen–air mixture. At the end of surgery, fentanyl 20 μg and ketorolac 30 mg were administered for initial pain control, and residual neuromuscular blockade was reversed with neostigmine and atropine.

All surgical procedures were performed using a multiport laparoscopic technique. At the end of each operation, CO2 was evacuated according to standard protocol. Pain intensity, as an indicator of acute postoperative pain, was recorded for each patient during the first 24 hours using the Visual Analog Scale (VAS). Vital signs, including blood pressure, heart rate, oxygen saturation, and respiratory rate, were measured every 40 minutes during the recovery room stay and subsequently at 2, 4, 6, 12, 18, and 24 hours after discharge from recovery, resulting in a total of seven measurement time points.

Statistical Analysis

All data were analyzed using SPSS version 25 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation, while categorical variables are expressed as frequency (percentage). Baseline quantitative variables were compared between the two groups using the independent-samples t-test, and categorical variables were compared using the chi-square test. To evaluate changes in pain intensity over time and assess the effect of the intervention, repeated-measures analysis of variance (repeated-measures ANOVA) was performed, examining the main effects of time and group, as well as the time × group interaction. When significant effects were observed, post hoc comparisons were conducted with Bonferroni adjustment. A p-value less than 0.05 was considered statistically significant for all analyses.

Ethical Considerations

The study protocol was implemented in accordance with the principles of the 1975 Declaration of Helsinki, as revised in 2013, and was approved by the Ethics Committee of Tabriz University of Medical Sciences prior to the start of data collection (ethics code: IR.TBZMED.REC.1404.405). The trial was also registered with the Iranian Registry of Clinical Trials (IRCT2019325043107N73). Before enrollment, all patients signed a written informed consent form after receiving a comprehensive explanation of the study objectives, potential benefits, and possible risks. Participants were also assured that

their personal information would remain confidential.

Results

Comparison of baseline and demographic characteristics revealed no statistically significant differences between the vitamin C and control groups across any of the variables assessed. The mean age was comparable between the two groups (*P* = 0.712), and sex distribution did not differ significantly (*P* = 0.628). Similarly, body weight (*P* = 0.801), height (*P* = 0.814), body mass index (*P* = 0.652), ASA classification (*P* = 0.812), duration of surgery (*P* = 0.561), and duration of anesthesia (*P* = 0.674) were comparable between groups (Table 1).

Before conducting the repeated-measures analysis of variance, the required assumptions were examined. The Shapiro–Wilk test indicated that pain intensity at the different time points had an acceptable normal distribution (*P* > 0.05). However, Mauchly's test of sphericity revealed that the assumption of sphericity was violated (Mauchly's W = 0.71, *P* = 0.032); therefore, the Greenhouse–Geisser correction was applied to adjust the degrees of freedom (ε = 0.84).

Table 1. Comparison of Baseline and Demographic Characteristics between the Two Study Groups

Variable	*Control group (n = 35)*	*Vitamin C group (n = 35)*	*P value*
Age (years)	*46.11 ± 10.12*	*45.26 ± 9.84*	*0.712**
Sex (male/female)	*16/19*	*14/21*	*0.628***
Weight (kg)	*72.40 ± 9.15*	*71.85 ± 8.92*	*0.801**
Height (cm)	*166.90 ± 7.65*	*167.32 ± 7.48*	*0.814**
Body mass index (BMI, kg/m²)	*26.01 ± 3.22*	*25.68 ± 3.14*	*0.652**
ASA class I/II	*21/14*	*22/13*	*0.812***
Duration of surgery (min)	*70.12 ± 13.05*	*68.45 ± 12.30*	*0.561**
Duration of anesthesia (min)	*84.20 ± 15.01*	*82.74 ± 14.18*	*0.674**

** Independent-samples t-test;*

*** Chi-square test*

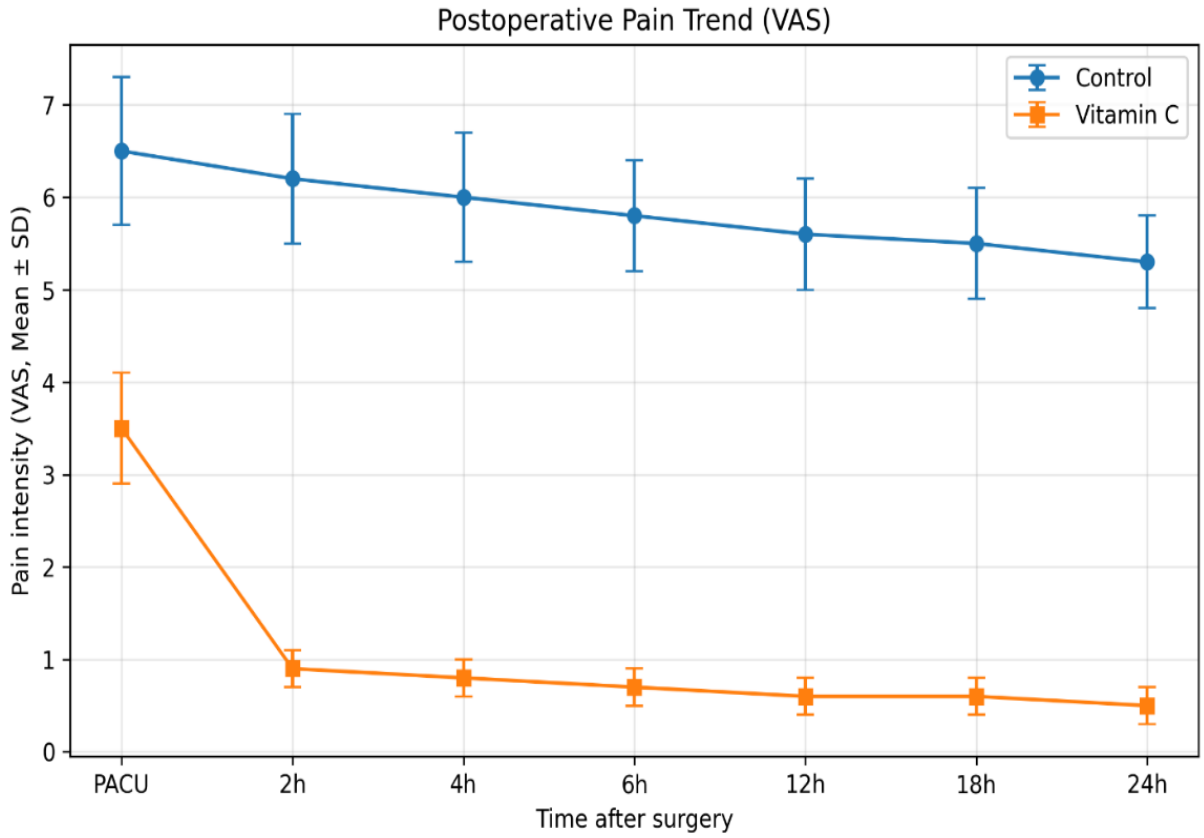

Figure 1. Comparison of acute postoperative pain intensity at various time points between the two groups.

Repeated-measures analysis of variance demonstrated a significant main effect of time on postoperative pain intensity (SS = 128.64, df = 4.20, MS = 30.63, F = 45.72, *P* < 0.001, partial η^2 = 0.40), indicating that pain severity significantly decreased over time in both groups. The main effect of group was also significant (SS = 36.18, df = 1.00, MS = 36.18, F = 18.95, *P* < 0.001, partial η^2 = 0.22), showing that patients who received vitamin C experienced lower overall pain intensity compared to those in the control group.

In addition, the time-by-group interaction was significant (SS = 52.47, df = 4.20, MS = 12.49, F = 16.84, *P* < 0.001, partial η^2 = 0.28), indicating that the pattern of pain change over time differed between the two groups. Pain reduction in the vitamin C group was faster and more sustained than in the control group. Based on Bonferroni-adjusted post hoc comparisons, pain intensity in the vitamin C group was significantly lower than in the control group upon arrival in the recovery room and at 2 (*P* = 0.011), 4 (*P* = 0.015), 6 (*P* = 0.019), 12 (*P* = 0.021), 18 (*P* = 0.029), and 24 (*P* = 0.042) hours after surgery. Overall, pain intensity decreased over time in both groups; however, the magnitude of reduction was greater in the vitamin C group, supporting the effectiveness of this intervention in reducing acute pain during the first 24 hours after laparoscopic cholecystectomy (Figure 1).

Discussion

The present study aimed to evaluate the effectiveness of intravenous vitamin C administration in preventing acute pain following laparoscopic cholecystectomy. The findings showed that vitamin C

administration in patients undergoing this procedure was associated with a significant reduction in the intensity of acute postoperative pain. This analgesic effect began in the early postoperative hours and persisted throughout the 24-hour follow-up period, with patients receiving vitamin C consistently reporting less pain than those in the control group. The persistence of this effect highlights the potential value of vitamin C in the prevention and management of acute postoperative pain and supports its inclusion in multimodal postoperative pain management protocols.[15]

Acute postoperative pain results from a complex interplay of tissue injury, activation of inflammatory pathways, and stimulation of both the peripheral and central nervous systems. Even in laparoscopic surgery, despite its minimally invasive nature, factors such as pneumoperitoneum, peritoneal stretching, and visceral manipulation can trigger the release of inflammatory mediators and activate nociceptive pathways. These processes promote inflammation and sensitize pain receptors, thereby determining the severity of postoperative pain.[16]

One of the key factors contributing to the intensification of postoperative pain is increased oxidative stress resulting from the generation of reactive oxygen species in response to surgical injury. These reactive molecules exacerbate inflammation and cellular damage, stimulate nociceptive nerve endings, and enhance the transmission of pain signals. Previous studies have demonstrated a direct association between the degree of postoperative oxidative stress and the level of pain reported by patients.[17]

Vitamin C, a potent water-soluble antioxidant, plays an important role in neutralizing reactive oxygen species and reducing oxidative damage. By suppressing oxidative stress, it helps reduce both local and systemic inflammation, thereby decreasing the stimulation of peripheral pain receptors. This mechanism may explain the early reduction in pain intensity observed in patients who received vitamin C.[18]

In addition to its antioxidant effects, vitamin C exhibits significant anti-inflammatory properties. By inhibiting the production of pro-inflammatory cytokines and modulating the inflammatory response induced by surgery, vitamin C may reduce the severity of postoperative inflammation. This attenuation of inflammation can limit peripheral sensitization and decrease the transmission of pain signals to the central nervous system.[19]

From a neurophysiological perspective, vitamin C is involved in regulating central nervous system function and modulating nociceptive transmission. It is involved in the synthesis and regulation of neurotransmitters such as norepinephrine and serotonin and may strengthen descending inhibitory pain pathways. Activation of these pathways can increase pain tolerance and reduce pain perception following surgery.[20]

Another proposed mechanism underlying the analgesic effects of vitamin C is its interaction with the endogenous opioid system. Evidence suggests that vitamin C may enhance the body's natural response to pain by increasing endorphin release or improving opioid receptor sensitivity. This mechanism may help reduce pain intensity without the need for higher doses of opioid analgesics.[21]

Vitamin C also plays an essential role in tissue repair and wound healing. It is necessary for collagen synthesis, and adequate availability of this vitamin promotes faster repair of injured tissues. More effective tissue healing can reduce the persistent stimulation of pain receptors at the surgical site, thereby decreasing both the severity and duration of postoperative pain.[22]

Taken together, these mechanisms suggest that vitamin C reduces acute postoperative pain through multiple complementary pathways, including antioxidant, anti-inflammatory, neuromodulatory, and tissue-reparative effects. The consistency of these findings with earlier reports in other surgical settings further strengthens the scientific rationale for using this intervention.[23]

One limitation of this study concerns the randomization procedure. Although patient allocation was primarily conducted using blocks of four, the final sample

size (n = 70) was not divisible by this block size; therefore, simple randomization was applied to the last two participants. Consequently, the randomization strategy was not implemented uniformly across the entire sample. While this issue was partially controlled by maintaining equal group sizes, the original study design could have avoided this limitation by selecting a different block size, such as blocks of two or a combination of variable block sizes. Future studies are recommended to determine the block size in advance according to the total sample size to ensure uniform participant allocation.

Conclusion

Given its favorable safety profile, low cost, and wide availability, vitamin C may be considered as part of a multimodal strategy for postoperative pain management. The findings of this study indicate that intravenous vitamin C is an effective and practical intervention for preventing acute pain following laparoscopic cholecystectomy and may contribute to improved clinical outcomes and an enhanced patient experience.

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