Effect of vitamin C on morphine use after laparoscopic cholecystectomy: a randomized controlled trial

Effet de la vitamine C sur l'utilisation de morphine après cholécystectomie par voie laparoscopique: une étude randomisée et contrôlée

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Abstract

Purpose We designed a randomized double-blind placebo-controlled trial to assess the role of a single prophylactic dose of vitamin C (2 g) po in reducing the consumption of opioids postoperatively in patients undergoing laparoscopic cholecystectomy.

Methods Eighty adult patients were allocated to receive 2 g vitamin C po or placebo approximately one hour prior to induction of anesthesia. Following laparoscopic cholecystectomy, patients received morphine patient-controlled analgesia for 24 hr. The following data were assessed postoperatively in the postanesthesia care unit at two, four, six, 12, and 24 hr: morphine consumption, verbal numerical rating scale scores for incisional pain and nausea/

vomiting, and pruritus and sedation scores. The primary outcome measure was 24-hr morphine consumption. Patient satisfaction was assessed before hospital discharge.

Results Morphine consumption was significantly lower in the vitamin C group vs the placebo group [16.2 (10.7) and 22.8 (13.8) mg, respectively; difference = 6.6 mg; 95% confidence interval, 1.1 to 12.1 mg; $P = 0.02$]. There was no difference in pain scores or side effects between the two groups. Satisfaction scores were similar in both groups.

Conclusion Our study showed that supplementation with vitamin C (2 g) po decreased morphine consumption in the postoperative period in patients undergoing laparoscopic cholecystectomy. (ClinicalTrials.gov number, NCT01322061).

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Résumé

Objectif Nous avons conçu une étude randomisée à double insu, contre placebo, pour évaluer l'effet d'une dose prophylactique unique de vitamine C (2 g) per os sur la réduction de la consommation des antalgiques morphiniques en postopératoire chez des patients subissant une cholécystectomie par voie laparoscopique.

Méthodes Quatre-vingt patients ont été répartis pour recevoir 2 g de vitamine C per os ou un placebo environ une heure avant l'induction de l'anesthésie. Après la cholécystectomie par voie laparoscopique, les patients ont reçu une analgésie contrôlée par le patient à base de morphine pendant 24 heures. Les données suivantes ont été évaluées en postopératoire en salle de réveil à 2, 4, 6, 12 et 24 heures: consommation de morphine, résultats des échelles verbales numériques pour la douleur liée à l'incision et pour les nausées/vomissements, et les scores de prurit et de sédation. Le principal critère d'évaluation

était la consommation de morphine en 24 heures. La satisfaction du patient a été évaluée avant son congé de l'hôpital.

Résultats La consommation de morphine a été significativement plus basse dans le groupe vitamine C que dans le groupe placebo (respectivement, 16,2 [10,7] et 22,8 [13,8] mg; différence = 6,6 mg; intervalle de confiance à 95 %: 1,1 à 12,1 mg; $P = 0,02$). Il n'y a pas eu de différences entre les deux groupes pour ce qui concernait les scores de douleur ou les effets indésirables. Les scores de satisfaction ont été comparables entre les deux groupes.

Conclusion Notre étude a montré qu'une supplémentation en vitamine C (2 g) per os a abaissé la consommation de morphine au cours de la période postopératoire chez des patients ayant subi une cholécystectomie par voie laparoscopique. (Numéro ClinicalTrials.gov: NCT01322061).

Despite advances in pain treatment, postoperative pain continues to be undertreated, perhaps due to the side effects of the commonly used pain medications. Opioids remain the golden standard treatment for postoperative pain despite the occurrence of sedation, ileus, and respiratory depression.¹ Non-steroidal anti-inflammatory drugs (NSAIDs) are usually used as adjuvants that may decrease the dosage of opioids and their related adverse events.² However, NSAIDs have their own side effect profiles, including but not limited to gastric ulceration, bleeding tendency, and nephrotoxicity.

Ascorbic acid, also known as vitamin C, is a water-soluble vitamin necessary for normal growth and development. It is a necessary component in the formation of collagen, which is important for healing skin and scar tissue, tendons, ligaments, and blood vessels.³ Vitamin C is also known for its antioxidant, neuroprotective, and neuromodulating effects.³⁻⁷ Clinical studies have shown that oral supplementation of vitamin C in the range of 0.5-3 g might play a role in pain treatment without any significant side effects. In a double-blind placebo-controlled crossover study, Jensen *et al.*⁸ have shown that 1 g of vitamin C reduced pain and improved function in patients with hip and knee osteoarthritis. Besse *et al.*⁹ showed that 1 g of vitamin C started on the day of surgery and continued for 45 days postoperatively was effective in reducing complex regional pain syndrome symptoms in high-risk patients after wrist, ankle, and foot surgery. Chen *et al.*¹⁰ showed that patients with post herpetic neuralgia had a lower plasma concentration of vitamin C. Moreover, when vitamin C was administered at 50 mg·kg⁻¹, maximum dose 2.5 g·day⁻¹ iv every other day for three days, there was a decrease in spontaneous but not brush-evoked pain. Kirk *et al.*¹¹ have shown that the use of a combination of antioxidants, among which was vitamin C, reduced pain and improved quality of life in patients with chronic pancreatitis.

However, we were interested in evaluating the potential role of vitamin C in reducing acute pain, hence, we designed a randomized placebo-controlled trial to assess the role of a single prophylactic dose of oral vitamin C (2 g) in reducing the consumption of opioids during the first 24 hr (primary outcome) in patients undergoing laparoscopic cholecystectomy. Both the patients and the investigators collecting the data were blinded to group allocation. Pain intensity and side effects were analyzed as secondary outcomes.

Method

Patient population

Patients (aged 18-75 yr, American Society of Anesthesiologists physical status class I-III) scheduled for elective laparoscopic cholecystectomy were included in this study. Exclusion criteria included patients allergic to morphine, patients with a history of chemical dependence, chronic pain state, obstructive sleep apnea, severe asthma, chronic obstructive pulmonary disease, or gastroesophageal reflux, or those receiving anti-inflammatory drugs during the 24 hr immediately preceding surgery. This study was approved by the Institutional Review Board at the American University of Beirut Medical Center (October 2011, Approval number: ANES.GK.06), and all patients gave written consent before participation in the study.

Randomization and intervention

Eighty-four patients were randomized using a computer-generated randomization table that was produced by the research assistant (B.M.). Group allocation was concealed in sealed opaque envelopes that were numbered and opened sequentially after patient consent had been obtained. Patients were then assigned to receive either 2 g of vitamin C (Redoxon, Bayer HealthCare, Toronto, ON, Canada) or a placebo. Vitamin C effervescent tablets were dissolved in 15 mL of water. An equivalent volume of carbonated orange beverage having exactly the same colour and taste was used for placebo. The drug or placebo was administered approximately one hour prior to surgery.

All patients were premedicated with midazolam 2 mg iv and monitored using a three-lead electrocardiogram, non-invasive blood pressure, esophageal temperature probe, ET_{CO₂}, and oxygen saturation. Induction was achieved in sequence using lidocaine 1.5 mg·kg⁻¹, fentanyl 2 µg·kg⁻¹, and propofol 2 mg·kg⁻¹. Rocuronium 0.6 mg·kg⁻¹ was used to facilitate tracheal intubation. Sevoflurane (2-4%) in a mixture of oxygen and air was used for maintenance of anesthesia. Fentanyl supplementation was used to maintain

blood pressure and heart rate within 25% of baseline values. At the end of surgery, neuromuscular blockade was reversed with neostigmine and glycopyrrolate. All patients received ondansetron 4 mg *iv*.

Outcome and follow-up

Upon arrival in the postanesthesia care unit (PACU), patients were started on an intravenous morphine patient-controlled analgesia (PCA) pump. The PCA bolus dose was set at 1 mg with a lockout time of six minutes, a four-hour limit of 30, and no basal rate. Patients in both groups were educated preoperatively on the use of the PCA. Morphine consumption was retrieved from the PCA pump report. Paracetamol 1 g *iv* every six hours was prescribed upon patient request for breakthrough pain. Prior to discharge from the PACU, a 5 mL blood sample was collected from each patient to measure vitamin C plasma concentration.

All patients were evaluated for pain, sedation, nausea, vomiting, pruritus, morphine consumption, and vital signs every 15 min during their stay in the PACU and at two, four, eight, 12, 18, and 24 hr after surgery. These evaluations were performed by a blinded anesthesiologist who was not involved in the study; preoperative staff, operating room staff, recovery room staff, ward nurses, and statisticians were also blinded. Patients reported pain intensity using the verbal numerical rating scale (NRS) where 0 = no pain and 10 = worst pain intensity.

Sedation was monitored using the Ramsey scale. Patients reported the intensity of nausea/vomiting using the NRS, where 0 = no nausea and 10 = the worst nausea as well as vomiting. The number of vomiting episodes was recorded as well as the number of antiemetics received. Moreover, the incidence of pruritus was reported by patients using a none-mild-moderate-severe scale. Before discharge from hospital, all patients were asked to report their overall satisfaction regarding postoperative pain management using the following scale: excellent, good, fair, or poor.

Statistical analysis

The primary outcome measure was 24-hr morphine consumption. A pilot study showed that mean morphine consumption in the placebo group was 25 mg with a standard deviation (SD) of 11.5 mg. We targeted an effect size (i.e., mean change of the variable divided by the SD of that variable) of at least 0.65, which is considered a medium to large change.^{12,13} This corresponded to a 30% reduction in the primary outcome. Based on a power analysis with a type I error of 5% (two-sided), a type II error of 20%, and a clinical significance of 30% reduction in the amount of morphine required between the two

groups, at least 39 patients were needed per group.¹⁴ Therefore, the target number of patients to recruit in each group was 40.

Continuous data were reported as mean (SD) and analyzed using Student's two-sample *t* test. Categorical data were reported as numbers and percentages and were analyzed using Chi square. Fisher's exact test was used whenever the expected values in two of the cells of a contingency table were below 5. Skewed data were reported as median and range and analyzed using the Mann-Whitney *U* test. All reported *P* values are two-sided. All analyses were performed using SPSS® version 19 (Chicago, IL, USA).

Results

One hundred thirty-eight patients were screened for the study from November 2010 to July 2011. Twenty-three patients refused to participate in the study, whereas 31 patients were excluded for not meeting the inclusion criteria. Eighty-four patients were randomized to receive either one single dose (2 g) of vitamin C or placebo (Fig. 1). Four patients were further excluded for protocol violation (wound infiltration with bupivacaine), one patient from the vitamin C group and three patients from the placebo group. Eighty patients (40 in each group) were analyzed. Patients' and operative characteristics are reported in the Table.

There was no difference in morphine consumption between the two groups during their PACU stay [7.9 (4.7) mg in the placebo group vs 7.5 (6.7) mg in the vitamin C group]. After the PACU stay, patients in the placebo group consumed more morphine than patients in the vitamin C group to achieve adequate pain relief. The average total morphine consumption during the first 24 hr postoperatively was significantly higher in the placebo group than in the vitamin C group [22.8 (13.8) mg vs 16.2 (10.7) mg, respectively; difference = 6.6 mg; 95% confidence interval 1.1 to 12.1 mg; *P* = 0.02] (Figs 2 and 3). The median number of intravenous paracetamol doses consumed for supplemental analgesia during the first 24 hr was similar between the vitamin C and the placebo groups [1 (0-5) vs 1 (0-5); *P* = 0.61].

Postoperative incisional pain scores at 15, 30, 45, and 60 min and at two, four, eight, 12, 18, and 24 hr were similar between the two groups. Except for the first 30 min, the incisional median pain scores achieved in both groups were < 3.

None of the patients ingested vitamin C on a regular basis. Blood samples for vitamin C plasma levels were drawn post randomization at 236 (71) min in the vitamin C group vs 216.2 (54.4) min in the placebo group. Patients randomized to the vitamin C group had a significantly

Fig. 1 CONSORT flow diagram **Table** Patients' and operative characteristics

	Placebo (n = 40)	Vitamin C (n = 40)
Age (yr)	47.5 (16.7)	45.9 (15.1)
Sex (Female/Male)	25/15	28/12
Weight (kg)	79.3 (13.5)	75.8 (14.1)
Height (cm)	165 (10.6)	165.4 (6.7)
ASA class		
I	23	24
II	14	12
III	3	4
Number of smokers	16	17
Intraoperative fentanyl consumption (µg)	213.2 (63.6)	226.9 (70.1)
Duration of surgery (min)	80 (35-170)	80 (45-190)
Time in PACU (min)	60 (45-120)	60 (45-120)

Data are presented as means (standard deviation), numbers or median (range). ASA = American Society of Anesthesiologists' physical status; PACU = postanesthesia care unit

Fig. 2 Cumulative morphine consumption at different time intervals. Values represent means and standard deviations; * $P = 0.02$. PACU = post anesthesia care unit **Fig. 3** Dot plots showing cumulative 24-hr morphine consumption in milligrams in patients from both groups. The thick bars represent the sample means of the group

higher vitamin C plasma level than those randomized to the placebo group [$10 (5) \text{ mg} \cdot \text{L}^{-1}$ vs $4 (3) \text{ mg} \cdot \text{L}^{-1}$, respectively; $P < 0.001$].

Median nausea scores were zero in both groups. Eight patients in the vitamin C group and five patients in the placebo group vomited during the first 24 hr, and the median (range) number of antiemetics consumed was 0 (0-2) in the vitamin C group and 0 (0-3) in the placebo group. Sedation scores were comparable between the two groups at all time intervals. The highest sedation score recorded was 2. No clinically significant pruritus occurred in either

group, and the highest pruritus score reported in either group was 1. Ninety-five percent of the patients in the vitamin C group reported a satisfaction score of excellent or good vs 90% of the patients in the placebo group.

Discussion

Our study showed that oral supplementation with 2 g of vitamin C decreased the postoperative morphine consumption in patients undergoing laparoscopic cholecystectomy. There was no difference in morphine consumption between groups during the PACU stay. The decrease in morphine consumption started post discharge from the PACU, which coincided within four hours from vitamin C intake. The incisional NRS scores were comparable between the two groups at all time intervals, and there were no differences in the sedation, vomiting/nausea, itching, and overall patient satisfaction scores.

The antinociceptive effect of vitamin C and its site of action are not well understood; however, vitamin C has several potential functions, such as antioxidation and neuromodulation, which may play a role in pain relief. Kim *et al.*⁵ showed that reactive oxygen species (ROS) play a role in neuropathic pain mediation, and they also showed that the use of ROS scavengers ameliorated the mechanical discomfort in a single nerve ligation pain model in rats. Thus, vitamin C may play a role in antinociception through its antioxidative properties. Furthermore, Rokyta *et al.*¹⁵ showed that the combination of antioxidants, such as vitamins A, C, and E, and analgesics normalized the tail-flick latency in a mechanically induced animal pain model. The authors attributed this antinociceptive effect to the reduction in the ROS. Moreover, they suggested that the administration of antioxidants in pain treatment may decrease the doses of analgesics.

In addition to its antioxidative function, vitamin C was found to have a neuromodulating function. It was shown to modulate the neurotransmission of dopamine and glutamate through the redox changes on the N-methyl-D-aspartate (NMDA) receptor.^{3,16} Rosa *et al.*¹⁷ have shown that vitamin C has an antinociceptive effect in chemically induced animal pain models, and the authors suggested an inhibitory effect of vitamin C on the ionotropic NMDA receptor. However, no inhibitory effect was shown on the metabotropic NMDA receptor.^{6,7}

Vitamin C is also important in the biosynthesis of neurotransmitters. It acts as a cofactor for dopamine β -hydroxylase, which is the rate-limiting step in the formation of norepinephrine^{18,19} and is involved in cholinergic and GABAergic transmission.^{20,21}

These neurotransmitters are well known to be the main components of the inhibitory pain pathway.²²

In our study, the absorption of vitamin C was evidenced by the higher plasma level in the vitamin C group compared with the placebo group. The pharmacokinetics of vitamin C are well described in the literature. The peak serum level of vitamin C occurs at about four hours after administration.^{23,24} In our study, the decrease in morphine consumption started post PACU discharge, approximately four hours after administration of vitamin C, which may correspond with the onset of its analgesic effect.

The dose and route of administration of vitamin C were based on a review of the different doses used in clinical trials. The doses ranged from 0.5 g to 3 g,^{8,25,26} hence, we chose a 2 g dose in our study. However, dose-finding studies may be required in future to find the optimal oral dose of vitamin C. Also, the route of administration, oral vs parenteral, which would result in optimal serum levels, needs to be determined.

In the current study, both groups had adequate pain relief as evidenced by the comparable NRS scores for incisional pain. However, this result was achieved at the expense of significantly higher morphine consumption in the placebo group. With PCA, patients in both groups had immediate access to morphine and were able to obtain adequate pain relief. This indicates that oral supplementation with 2 g of vitamin C has a dose sparing effect on morphine consumption. However, this result needs to be confirmed in future more painful surgical models.

Although there was a significant decrease in morphine consumption between the two groups, there were no significant differences in nausea/vomiting and pruritus. This could be due to the low morphine requirements for such procedures and hence the lower incidence of side effects.²⁷ In addition, our study was not powered to detect differences in the side effect profile.

There are a number of limitations in our study. We did not assess the vitamin C baseline plasma concentration in both groups. However, post randomization plasma blood levels confirmed that significantly higher levels were indeed present in treated patients. In addition, we selected a surgical model that has relatively low postoperative pain intensity, and as such, a more painful surgical model may be needed to confirm our findings. Furthermore, we did not perform an intention-to-treat analysis because we did not collect data for the patients excluded after randomization; however, only four patients were excluded, which is unlikely to lead to a biased estimate of the treatment effect.

In conclusion, this is a unique study examining the effect of oral supplementation of vitamin C in an acute pain model. The results have shown that a 2 g oral dose of vitamin C decreased morphine consumption in the postoperative period in patients undergoing laparoscopic cholecystectomy. Future studies are needed to confirm our

findings and to determine optimal doses and routes of administration.

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Conflicts of interest None declared.

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