

Does The Vitamin C Have An Effect On Postoperative Pain after Laparoscopic Cholecystectomy

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Abstract

Possibility of oxidative stress protection in perioperative period plays its role in pain therapy and inflammation after surgical interventions. The aim of our study is to analyze the action effects of preoperatively ordained vitamin C on the level of antioxidative stress enzymes and the intensity of painful sensations after the elective laparoscopic cholecystectomy (LC).

Methods: In a prospective study we analyzed the painful sensations and measured the levels of antioxidative stress enzymes 48 hours postoperatively in patients undergoing elective LC. The 59 patients are divided into two groups: Group A – 30 patients who received vitamin C at a dose of 1,0 g iv preoperatively and Group B – 29 patients who not received vitamin C. For all patients postoperative analgesic combination have been ketorolac and tramadol. A visual analogue scale (VAS) was used to evaluate the pain every six hours postoperatively.

Results: Analyzing pain intensity in our patients during first two days postoperatively it was recorded pain lower than 3,5 in Group A and 4,5 VAS in Group B. There is found a statistically significant difference ($p < 0.05$) between the examined groups. Analysis of variance for repeated measurements (ANOVA) were found significantly higher values ($p = 0,000$) of SOD in patients who had previously been administered vitamin C (Group A) as compared to patients who had not previously been administered vitamin C (Group B).

Conclusion: Preoperatively intravenous administration of Vitamin C reduces pain and it can be effective adjunctive therapy for acute pain in the early postoperative period. Higher values of enzyme AOS postoperatively confirm the fact that Vitamin C contribute to reduction of oxidant stress.

Keywords: Postoperative Pain; Vitamin C; Oxidative Stress; Cholecystectomy

Introduction

Inadequate postoperative analgesia, manifested through physiological and endocrino-metabolic response, can affect the functioning of almost all organic systems and the increase of postoperative morbidity and mortality [1]. Despite all that is known, still over 50 percent of patients have severe pain after surgery around the world. Multimodal analgesia treats all aspects of pain pathway including stimulation, modulation, inflammation and psychological component, where combination of analgesics, co-analgesics and therapeutic procedures has aim to create a regime of synergistic control of the pain, which most efficiently protects patient from operative stress [2].

Surgical trauma after laparotomy triggers a series of cascade physiological reactions in the body leading to release of a range of inflammatory process mediators and oxidative stress [3]. Numerous antioxidant systems take part in neutralization of reactive types of nitrogen and oxygen, reducing damages of cells and present biomolecules to minimum [4]. Primary antioxidative protection consists of enzymatic and non-enzymatic components. Vitamin C (ascorbic acid) represents non-enzyme component of the antioxidative protection system. Possibility of protection from oxidative stress in perioperative period plays its role in pain therapy and inflammation decrease after surgical interventions [5,6].

The aim of our study is to analyze the action effects of preoperatively ordained vitamin C) and surgical incision on the level of enzyme AOS and the intensity of painful sensations during the early postoperative period, after the elective laparoscopic cholecystectomy (LC).

Methodology

Our work represents a prospective randomized study dealing with the evaluation of oxidative stress and pain intensity in 59 patients who had undergone an elective open cholecistectomy. According to ASA (American Society of Anesthesiologists) classification of the patients general condition the study included only patients who belong to groups with ASA score I-II. Inclusion criteria was age from 35 to 65, Body Mass Index from 18.5 to 29.9. Exclusion criteria was previous consumption of vitamin C and other antioxidants or patients who have been on any types of diets. Study did not include patients who had contraindications for the use of vitamin C (ASA I-II).

The 59 patients are divided into two groups

Group A - 30 patients who received vitamin C at a dose of 1,0g iv preoperatively 45 min before introduction of general anesthesia and Group B - 29 patients who not received vitamin C. Random numbers were generated by computers. Patients with even numbers were received vitamin C, patients with an odd number were received the same amount of physiological solution.

There are different opinions about doses of intravenous of vitamin C on surgery patients but according to the guidelines of our hospital there was used a dose of vitamin C of 1.0g.

Anesthesia and monitoring

The protocol of preoperative preparation, monitoring and general anesthesia was standardized. As for medication, all patients received intramuscularly 0,1 mg/kg i.m. of midazolam, 45 before the operation. As an anesthetic for the induction into general endotracheal anesthesia tiopental-natrium in dose of 5 mg/kg was used, and as a relaxant suxamethonium hydrochloride in dose of 1,5 mg/kg as the introduction into in anesthesia, together with fentanyl/ 0,1 mg before intubation. As an analgetic during surgery fentanyl in dose of 0,005 mg/kg was used, with a repetition in dose of 0,1 mg, depending on clinical parameters, and pancuronium-bromide in dose of 0,05 mg/kg to maintain relaxation. During surgery patients received Ringer lactate solution in dose of 5-10 ml/kg/h.

In all the patients the basic non-invasive hemodynamic monitoring was carried out during surgery. The start and the end of the operation was recorded referring to the time of intubation and extubation of the patient.

Surgical technique

All patients were subjected to a laparoscopic cholecystectomy, well-known surgical technique and all surgeries were performed by the same surgeon.

Analgesic treatment

Anti-inflammatory non-steroidal analgetic – ketorolac was administered against pain to all the patients intravenously at a dose of 30 mg 10 minutes before the end of the operation and then at 6h i.v. postoperatively. Patients in Group B received only ketorolac, without vitamin C. In the case of severe pain, we added a tramadol in the dose of 50 mg at the patient's request.

Evaluation of oxidative stress

Testing effects of oxidative stress was performed at regular intervals. Antioxidant status was determined before taking the medication and before operation, as well as during analgetic and antioxidant treatment in four time intervals: preoperative time (T1), before taking any pharmacological agents, immediately after surgery «0»h (T2), 24 hours postoperative (T3) and 48 hours (T4), based on values of enzyme AOS: superoxide-dismutase, catalase, glutathione-peroxidase and glutathione-reductase (SOD, GSPHx, CAT, GR) from erythrocytes of the examinees. Changes of the values of those enzymes were compared, in relation to the two groups of the patients (Group A – ketorolac and vitamin C, Group B – only kontrolac).

Evaluation of Pain

Assessment Evaluation of pain intensity and therapeutic effect check was assessed according to visual analogue scale (VAS) every six hours postoperatively.

Results

Related to gender distribution of patients, females dominated significantly: 45 female patients or 76%. The average age of the patients was 54. There was not a significant difference between the age and gender structure of patients in analyzed groups ($p > 0,05$).

Antioxidative stress enzymes

Analysis of variance for repeated measurements (ANOVA), where one parameter is time and the other ordained drugs (vitamin C), statistically highly significant difference was found in values of SOD, CAT, GSPHP and GR ($p < 0,001$), in relation to both parameters (Table 1).

	Medications	SOD	CAT	GSH-Px	GR
(T1) preop	Ketorolak + vit C (Gr A)	4121	16,11	18,63	5,82
	Ketorolak (Gr B)	3590	14,74	13,82	4,53
(T2) Immediately postop	Ketorolak + vit C (Gr A)	4308	15,98	18,01	6,05
	Ketorolak (Gr B)	2730	13,57	14,90	5,80
(T3) 24 h postOp	Ketorolak + vit C (Gr A)	3988	15,96	19,68	5,73
	Ketorolak (Gr B)	3013	13,50	15,59	5,65
(T4) 48 h postOp	Ketorolak + vit C (Gr A)	4324	16,13	17,54	5,98
	Ketorolak (Gr B)	3240	13,50	16,65	5,75

Table 1: Values of antioxidative stress enzymes in relation to prescribed medications.

At all times postoperatively were found significantly higher values of SOD, CAT, GSPHP and GR in patients who had previously been administered vitamin C as compared to other patients ($p < 0,001$) (Table 1).

Evaluation of postoperative pain

Pain was evaluated and analysed in patients in regular intervals during following postoperative 48 hours. Patients in both groups have had at average pain lower than 4 VAS (mild pain).

Analysis of variance for repeated measurement showed significant differences between the examined patient groups as regards of pain intensity in postoperative period (Kruskal-Wallis Test, $p < 0,05$) (Table 2 and Figure 1).

Pain	Medications	Mean (VAS)
The end of surgery	Ketorolak+vit C	1.50
	Ketorolak	2.41
	Summary	1.80
After 6 h postop	Ketorolak+vit C	3.36
	Ketorolak	4.55
	Summary	3.96
After 12h postop	Ketorolak+vit C	3.07
	Ketorolak	3.65
	Summary	3.36
After 18 h postop	Ketorolak+vit C	2.62
	Ketorolak	2.86
	Summary	2.74
After 24h postop	Ketorolak+vit C	2.90
	Ketorolak	2.82
	Summary	2.86
After 32 h postop	Ketorolak+vit C	2.96
	Ketorolak	3.13
	Summary	3.05
After 40 h postop	Ketorolak+vit C	1.83
	Ketorolak	2.86
	Summary	2.35
After 48 h postop	Ketorolak+vit C	1.51
	Ketorolak	1.65
	Summary	1.58

Table 2: Pain intensity in relation to ordained medications.

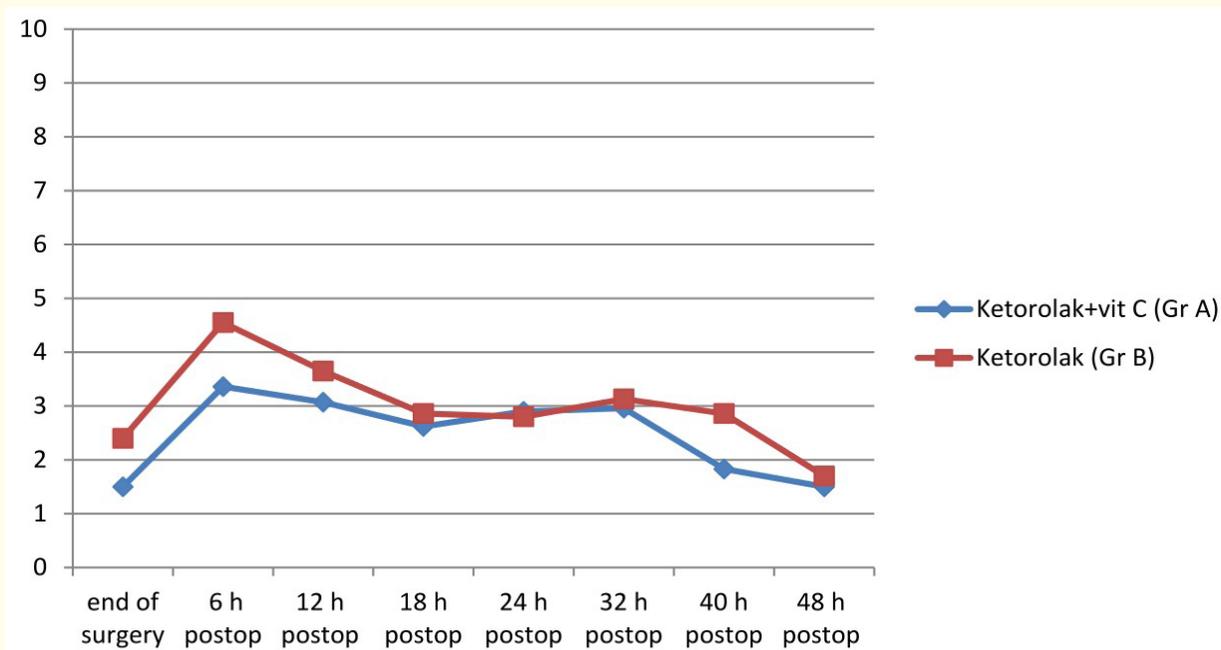


Figure 1: Pain intensity (VAS) in relation to ordained medications.

Pain of strongest intensity was present 6 hours after surgical intervention, then it decreased as time was passing (Table 2). The strongest pain within 6 hours postoperatively had the patients who were receiving ketorolac (VAS 4,5), while the pain of weakest intensity in almost all times, with most standardized curve had the patients who had received ketorolac with vitamin C (VAS < 3,3).

We did not find a statistically significant difference in the values of vital functions (arterial blood pressure, heart rate, breathing frequency) among comparable groups (A and B) ($p > 0,05$).

Opioids consumption

There was no statistically significant difference between groups A and B in relation to consumption of fentanyl intraoperatively ($p > 0,05$). Patients who received vitamin C had a less number of request for opioid analgesics postoperatively (tramadol) but we did not found statistically significant differences ($p > 0,05$).

Discussion

Surgical/anesthetical trauma is associated with increased production of release of reactive oxygen species (ROS). It leads to cell damage and resulting in numerous complications such as: sepsis, myocardial damage and increased mortality [3,7]. Many authors described increasing parameters of the oxidative stress after various abdominal surgeries, especially in comparison with laparoscopic surgery [8]. After laparoscopic interventions systemic oxidative stress is weaker, but pneumoperitoneum, appearing after CO₂ insufflation, exercises negative effects on local oxidative stress and causes tissue hypoxia, which demands further clinical research. Both open and laparoscopic cholecistectomy cause moderate oxidative stress [9,10].

The highest inflammatory and oxidative stress is indicated in first days after surgery [11]. Response to stress during surgery changes under the influence of many factors, including surgery gravity and duration, surgical technique, anesthesia type. Data on effects of anesthetic and analgetic procedures upon metabolic response to operation in humans are various, even controverse [12].

Due to the fact that wide abdominal surgery cause production of immune ROS in abdomen, some authors suggest enteral introduction of antioxidative supplements (glutamine, cysteine, zinc, vitamin C, beta carotene, selenium [4,13]. Various studies have been conducted in animal and the humans to prove that Vitamin C can be used as a component of multimodal analgesia. Vitamin C is a water-soluble vitamin which exerts its anti-nociceptive properties through its antioxidant action by neutralizing the reactive oxygen species formed during the stress of surgery. The Vitamin C also plays a role in the modulation of the neurotransmitters binding to NMDA receptors such as glutamate, that is involved in sensitization of pain [7]. Therefore, Vitamin C should be useful in lowering pain. There are number of studies regarding the use of vitamin C as an antioxidant drug for various disorders [14]. Vitamin C (L-ascorbic acid) is the most effective hydro-soluble antioxidant. It easily releases and receives two hydrogen atoms, so, this reversible reaction offers it a role of a strong redox system. Absorbtion intensity is inversely proportional to the relative concentration of vitmin C in the digestive tract. At the introduction of asorbic acid up to 150 mg per day concentration in blood rises in correlation with the entered dose, while a higher introduction leads to intensifying of elimination via kidneys, after the needs of tissues are met. However, by entering large dose, under condition of iron overload, in the process of tissue destruction and release of metal from the complex with protein, vitamin C can demonstrate prooxidant effect [12].

Vitamin C requirement is increased in surgical patients, and the potential advantage of supplementation is to increase the plasma and tissue levels of vitamin C and thereby reduce oxidative stress [15]. Although some clinical benefits of high-dose vitamin C supplementation have been shown in the critically ill, the optimal dose for supplementation and the clinical benefits remain to be investigated in surgical patients [6,7].

According to different studies perioperative vitamin C supplementation has an important play of the endogenous antioxidant defense and reduction in postoperatively morphine utilization. According to more study, administration of vitamin C up to 3 g IV pre and intraoperatively reduced postoperative pain without increased side-effects [14].

There is still no accurate of dose recommendation, administration method, and the length of vitamin C use. Additional studies are necessary to increase the level of evidence to determine the overall effectiveness and optimum dosage of vitamin C [12].

In our study, patients who were receiving only the analgetic ketorolac, without an antioxidative protection, have, in all times, lower antioxidative stress enzymes values unlike patients who received vitamin C ($p < 0,01$).

At all times postoperatively, statistically significantly higher SOD, GSHPx, CAT and GR values were found in patients who were preoperatively ordained vitamin C than in other patients ($p = 0,000$), which can be explained by protective effect of vitamin C. Many studies describe positive effect of vitamin C at various mechanisms of the developed increased oxidative stress in the body [16].

Especially significant is the difference 24 hours postoperatively in our patients who were receiving vitamin C unlike patients who not received vitamin C. Patients in this group showed the lowest oxidative stress 24 hours postoperatively.

Evaluation of pain

Despite huge technological advances in pain management, unrelieved pain remains common after surgeries [1]. There is estimated that up to 75% of patients do not achieve adequate pain relief postoperatively [2]. Acute inflammation induced by tissue damage causes ROS that have a major role in development of postoperative pain [17]. The major goal in the management of postoperative pain is to minimize the dose of medications to lessen the side effects while still providing adequate analgesia, because side effects of commonly used pain medications are known to be the reasons that could lead to inadequate postoperative pain treatment. One agent that can exert antinociceptive role and pain reducing effects is vitamin C [18].

According to various researches it was noticed that most painful operations are those in the chest and upper abdomen. Open surgeries are notably more painful than laparoscopic [9,10]. The origin of pain after laparoscopic cholecystectomy is multifactorial: pain arising from incision sites, pressure pneumoperitoneum, and the cholecystectomy [19].

Analyzing pain intensity in our patients we observed that during first two days postoperatively they had pain weaker than 4,5 VAS, which corresponds to moderate pain of the analogous scale (VAS). Immediately after the surgery pain measured approximately 2,2 VAS (mild pain). Patients of all groups experienced most severe pain 6 hours postoperatively. It was related with awakening and mobilization of patients. Six hours postoperatively the pain was most severe in the group B - patients who were receiving just ketorolac 4,55 VAS (moderate pain) and it was the pain of strongest intensity noticed postoperatively, during this research. In the rest of patients 6 hours postoperatively pain was weaker than 4 VAS and the mildest pain had the patients receiving vitamin C (3,2 VAS).

Conclusion

Preoperatively intravenous administration of Vitamin C reduces oxidative stress and pain and it can be used as a component of multimodal analgesia in the postoperative period.

There were found significantly higher values of antioxidant system enzymes (SOD, GSHP, CAT and GR) postoperatively in patients who had previously been administered vitamin C compared to other patients ($p < 0,001$).

Patients receiving vitamin C, have higher values of enzyme AOS postoperatively, which confirm the fact that Vitamin C contribute to reduction of oxidative stress and consequently inflammatory response and pain.

Patients who received vitamin C had a less number of request for opioid analgesics postoperatively (tramadol) but we did not found statistically significant differences ($p > 0,05$).

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