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Vitamin C premedication reduces postoperative rescue analgesic requirement after laparoscopic surgeries

Abstract

Background & Objectives: Pain is one of the common medical causes of delayed discharge from hospital. It causes adverse effect such as tachycardia, hypertension, myocardial ischemia, decrease alveolar ventilation, and poor wound healing. The reduction of pain may prevent these adverse effects and enhance early discharge from hospital. The premedication with oral vitamin C was assumed to reduce postoperative pain and rescue analgesic requirement in patients after laparoscopic surgeries.

Material and Methods: After approval from ethical committee and informed written consent, study was conducted on 200 patients of ASA physical status 1 and 2, who were scheduled for laparoscopic surgery. All the selected patients were divided in to 2 groups. Group 1 received oral vitamin C 2 gram and group 2 patients received placebo tablets in night and 2 hour before surgery. After premedication Patients were explained about surgical procedure and visual analogue pain scale (VAS 0: no pain and VAS 10: worst pain). Anesthesia was induced with propofol 2mg/kg and vecuronium bromide 0.1mg/kg as muscle relaxant and maintained with oxygen, nitrous oxide (50:50) and isoflurane. Patients in both group received injection paracetamol 10mg/kg body weight 30 minutes before skin closure. Neuromuscular blockade was reversed and patients were shifted in postoperative recovery room. The data were recorded and analyzed.

Results: The physical variables of both group patients were statistically comparable. Mean heart rate, blood pressure VAS score were statistically different in early part of postoperative period. The postoperative analgesic consumption in group 1 patients were significantly low.

Conclusion: We concluded that use of vitamin C reduces early postoperative pain and consumption of fentanyl as rescue analgesic in postoperative period.

Keywords: anaesthesia, postoperative pain, vitamin C, rescue analgesic

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Introduction

Today laparoscopic surgery is common for operations including radical prostatectomy, nephrectomy, adrenalectomy and other complex surgeries. The patients having laparoscopic surgeries experience postoperative pain, especially in the upper and lower abdomen, back and shoulder region. Pain intensity usually peaks during the first postoperative hours and usually declines over the following two to three days.. It is important to prevent adverse effect such as tachycardia, hypertension, myocardial ischemia, decrease in alveolar ventilation, and poor wound healing caused by pain. Various studies has been conducted in animal and The humans to prove that Vitamin C can be used as a component of multimodal analgesia. It 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.[1,2] In addition it has also role in modulating the sensitization of pain through its action on NMDA receptor. Laparoscopic surgeries are routinely performed therefore it is desirable to have proper pain control for the early discharge of patients from hospital.

Material and methods

After approval from Institute research ethical committee and patient informed written consent, a prospective randomized double blind study was conducted on 200 patients of ASA physical status 1 and 2, age between 18 to 75 years who were scheduled for laparoscopic surgeries. The patients were excluded from study who refused to participate in study and Patients who have chronic pain and received anti inflammatory drug 24 hour before surgery. All the selected patients were divided in to 2 groups. Group 1 received vitamin C 2gram and group 2 patients received placebo tablets in the night and 2 hour before surgery. All patients were given tablet ranitidine 150mg and tablet metoclopramide 10 mg in evening and 2 hour before surgery. Patients were explained about surgical procedure and visual analogue pain scale (VAS, 0: no pain and VAS 10: worst pain). In operative room monitors (ECG, noninvasive blood pressure, SpO2 probe, EtCo2) were attached and base line parameters were recorded. Injection fentanyl 2microgm /kg and injection midazolam 30 micro gm/kg body weight given before induction. Anesthesia was induced with propofol 2mg/kg and vecuronium bromide 0.1mg/kg as muscle relaxant. After intubation anesthesia was maintained with oxygen, nitrous oxide (50:50) and isoflurane. Patients in both group received injection paracetamol 10mg/kg body weight 30 minutes before skin closure. Neuromuscular blockade was reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.02mg/kg intravenously. Patients were transferred to postoperative recovery room after adequate recovery. Pain severity was assessed using VAS score. Hemodynamic parameters and VAS score were recorded at 0 min30 min, 60 min, 90min, 120 min and 240 minutes in postoperative period. Injection fentanyl 25 microgram IV was given as rescue analgesic when patient

had VAS score > 4. The data were analyzed statistically and p value < 0.05 was considered significant.

Results

The mean age of group 1 patients was 46.22±11.39 and group 2 patients was 44.49±11.26. The mean weight of group 1 patients was 57.09±9.70 and group 2 patients was 58.04±10.06 which is statistically comparable (Table 1). The age, sex, body weight and co-morbid conditions like diabetes, hypertension, asthma, allergy and ASA physical status of both group patients were comparable (p value > 0.05). The mean heart rate in Group I receiving Vitamin C tablets was 85.65±15.74 as compare to 93.31±17.24 in Group II receiving placebo tablets (Table 2).

Table 1 Age, sex, comorbidity and ASA physical status of the patients

S. No	Variables	Group 1	Group 2	P value
1	Age (years)	46.22±11.39	44.49±11.26	0.282
2	Sex			
	Males	34	28	0.359
	Females	66	72	0.359
3	Comorbidities			
	Diabetes	13/100	9/100	0.366
	Hypertension	16/100	22/100	0.279
	Asthma	5/100	7/100	0.552
	Allergy	5/100	11/100	0.118
4	ASA physical status			
	1	67	70	p=0.723
	2	33	30	p=0.723

ASA, American society of anesthesiologists

Table 2 Mean heart rate at different time interval

Time interval	Group 1 Mean±SD	Group 2 Mean±SD	t-value	p-value
HR_0	86.18±16.66	85.88±12.47	0.144	0.886
HR_30_min	85.65±15.74	93.31±17.24	-3.273	0.001
HR_60_min	83.81±14.61	85.73±13.41	-0.966	0.335
HR_90_min	82.42±14.51	82.74±11.64	-0.169	0.866
HR_120_min	81.26±14.26	82.72±11.55	-0.792	0.429
HR_240_min	81.73±13.81	81.27±11.97	0.25	0.803

HR, heart rate

Table 3 Mean Systolic Blood Pressure at different time interval

Time interval	Group 1 Mean±SD	Group 2 Mean±SD	t-value	p-value
SBP_0	119.59±15.39	120.04±12.04	-0.23	0.818
SBP_30_min	120.65±12.04	126.52±13.57	-3.227	0.001
SBP_60_min	117.25±12.49	119.25±11.69	-1.164	0.246
SBP_90_min	116.04±12.32	116.99±10.72	-0.58	0.563
SBP_120_min	114.74±11.35	115.29±11.09	-0.347	0.729
SBP_240_min	114.06±11.95	114.47±10.42	-0.258	0.797

SDP, systolic blood pressure

The mean Systolic and Diastolic blood pressure in Group I receiving Vitamin C tablets was 120.65±12.04 and 126.52±13.57 in Group II receiving placebo tablets. There is significant difference between the groups except at 30 min with p value < 0.001 (Table 3 & 4). VAS score in group 1 patients receiving vitamin C at immediate post operative was 2.64±1.13 and 3.72±1.63 in group 2 patients. At 30 min VAS score was 2.14±0.51 while in group II was 2.88±1.07. There was a statistically significant difference between the groups in VAS measured at 30 min with p value <0.001. The VAS score at 60, 90, 120 and 240 minute was statistically comparable (Table 5). In Group I, 6 patients required rescue analgesic whereas 41 patients in Group II required rescue analgesic at 30 minute with p value <0.001. In group 1 total 21 patients required 1 dose of rescue analgesic and in group 2, total 67 patients required 1 dose of fentanyl as rescue analgesic in 4 hour of postoperative stay which was statistically significant as shown in Table 6. The postoperative analgesic requirement at 60 min, 90 min, 120 min, 240 min were not statistically significant because the patients in Group II who had perceive pain, received bolus of rescue analgesics hence there was no difference between them.

Table 4 Mean Diastolic Blood Pressure at different time interval

Time interval	Group 1 Mean±SD	Group 2 Mean±SD	t-value	p-value
DBP_0	76.78±11.48	74.61±8.89	1.494	0.137
DBP_30_min	80.00±9.37	84.34±11.89	-2.858	0.005
DBP_60_min	77.53±9.26	76.52±9.16	0.769	0.443
DBP_90_min	75.61±8.13	74.32±7.81	1.137	0.257
DBP_120_min	74.23±8.06	72.50±7.49	1.57	0.118
DBP_240_min	74.15±8.95	72.01±7.85	1.793	0.074

DBP, diastolic blood pressure

Table 5 Mean VAS at different time interval

Time interval	Group 1 Means'	Group 2 Mean ± SD	t-value	p-value
VAS_Immediate postoperative	2.64±1.13	3.72±1.63	-5.433	<0.001
VAS at 30 min	2.14±0.51	2.88±1.07	-6.21	<0.001
VAS at 60 min	2.08±0.39	2.18±0.57	-1.434	0.153
VAS at 90 min	2.06±0.34	2.02±0.20	1.008	0.315
VAS at 120 min	2.04±0.28	2.02±0.20	0.579	0.563
VAS at 240 min	2.14±0.51	2.02±0.20	2.18	0.03

VAS, visual analogue scale

Table 6 Rescue analgesic requirement in postoperative period

S.No	Postoperative Rescue analgesic at	Group 1	Group 2	P Value
1	0 minute	25	63	< 0.001
2	30 minutes	6	41	< 0.001
3	60 minutes	4	9	0.152
4	90 minutes	3	1	0.312
5	120 minutes	2	0	0.497
6	240 minutes	6	0	0.029

Discussion

During laparoscopic surgery creation of pneumoperitoneum increases systemic vascular resistance and blood pressure due to nociception.[3] This nociception causes increased morbidity, prolonged hospitalization and delayed recovery causes financial problems.[4] To attenuate pain response during the laparoscopic surgeries, a wide variety of agents are being used both during premedication and induction. Various studies have shown that preemptive analgesia causes attenuation of signals entering spinal cord, which is much more effective than controlling pain after its induction.[5] Different type of treatments have been reported for pain relief. Recently, multimodal analgesia approach has been suggested to manage the postopera¬tive pain. Acute inflammation induced by tissue damage causes release of reactive oxygen species that have a major role in development of

postoperative pain. Various studies has been conducted in animal and The humans to prove that Vitamin C can be used as a component of multimodal analgesia. It 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.[1,2] 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.[6,7] The NSAIDS and other conventional analgesics like narcotics and other newer analgesic agents when used at their usual doses have significant side effects that restricts the physician to use them. The concept of multimodal analgesia is to reduces side effects caused by higher dose of single agent. More ever vitamin C is water soluble so there is less incidence of toxic symptoms produced even at high doses provided the renal function is adequate. In our study vitamin C had significantly reduced the VAS score at immediate postoperative and at 30 minutes. The number of patients required rescue analgesic at o minute and 30 minutes were also significantly low in vitamin C group patients. At 60 minute and on ward no significant difference was noted because most of the patients have received rescue analgesic. (63 patients at 0 min, 41 patients 30 min in group 2 and only 25patients at o min and 6 patients at 30min in group 1). Therefore no difference was observed at 60 minute (4 patient in group 1 and 6 patient in group 2) who required rescue analgesic. In postoperative period up to 4 hours total fentanyl consumption was also significantly less in group 1 (46 dose in group 1 and114 dose in group 2). In the later part of postoperative period (at 60, 90, 120, 240) there is no significant difference in VAS score because most of the patient received rescue dose of fentanyl at 30 minute of postoperative stay.

Kim HK et al.,[8] studied the role of reactive oxygen species in the causation of neuropathic pain in rat models by producing mechanical allodynia and treating them with antioxidants. This study suggests that systemic administration of non-toxic doses of free radical scavengers could be useful for treatment of neuropathic pain. Rebec GV et al.,[7] showed that ascorbate release in brain regulates the dopaminergic and glutamate transmission. They regulate the glutamate receptor binding on the NMDA receptors which is responsible of windup phenomenon of pain.

Rosa KA et al.,[9] reported that a single administration of vitamin C intra peritoneal significantly inhibited both the neurogenic (early phase) and inflammatory (late phase) pain responses of 2.5% formalin-induced paw licking in mice, in a dose-dependent manner. Additionally, vitamin C inhibited the biting responses induced by intrathecal administration of glutamate, NMDA, γ-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, kainate, and substance P in mice. These results may indicate that vitamin C produces antinociception by interacting with glutamate receptors.

Zollinger et al.,[10] did a study on 416 patients with wrist fractures to assess the role of Vitamin C in reducing complex pain regional syndrome type I (CPRS type 1). The result of this study was Vitamin C 500mg for 50 days reduces the prevalence of CPRS type I. Kanazi et al.,[11] did a study on 80 patients undergoing laparoscopic cholecystectomy with premedication dose of Vitamin C (2g) just one hour prior to surgery with postoperative morphine patient controlled infusion and analgesic consumption was assessed for 24 hours and result showed that Vitamin C reduces the analgesic requirement of morphine significantly.

Yet another study done by Zollinger et al.,[12] on 38 patients with trapezio metacarpal joint arthritis who were posted for arthroplasty were given Vitamin C 500mg/day two days preoperatively and fifty days postoperatively were found to have no occurrence of CPRS I. De las heras et al.,[13] conducted a study on chronic pancreatitis patients with a combination of micronutrients with antioxidant property like Vitamin C, methionine, beta carotene, Vitamin E and organic selenium to evaluate their antinociceptive effects and results concluded that there is a role of these antioxidants in pain reduction caused by pancreatitis.

Bharadwaj et al.,[14] conducted a study to evaluate the role of Vitamin C alone in 86 pancreatitis patients and found that Vitamin C supplementation reduces the number of painful days and reduced the amount of analgesics used per month in antioxidant group than control group. Kirk et al.,[15] conducted a study to evaluate the combined use of antioxidants like beta carotene, Vitamin C, Vitamin E and methionine on pain reduction and improvement in the quality of life assessed by SF-36 questionnaire in chronic pancreatitis patients. The study included 36 patients with treatment period of 20 weeks and it was found that in antioxidant group significant improvements in quality of life in terms of pain, physical, social functioning and general health perception compared to placebo group.

Visser et al.,[16] conducted a study using Vitamin C as a prophylactic drug in migraine patients and found that Vitamin C reduces the pain intensity and recurrence of the migraine attack than placebo group. The effect of topical application of disodium isostearyl 2-O-L-ascorbyl phosphate (DI-VCP),[17] a skin-permeable, amphiphilic ascorbic acid derivative when used it permeates the skin, and is then converted into ascorbic acid following hydrolysis by phosphatases present in the tissues.[17–19] Their evidence proved that DI-VCP ointment is a novel drug for treatment of neuropathic pain. The long-lasting anti-hyperalgesic activity of topical application of DI-VCP, suggests that this compound could be of therapeutic value in the treatment of clinical neuropathic pain. The several study results suggest that oxygen-derived free radicals are implicated in the mechanism of abdominal pain caused by alcohol-induced chronic pancreatitis and removing them results in a beneficial therapeutic effect. Laparoscopic surgeries are more popular these days because of cosmetic value and less duration of hospital stay. Therefore, achieving sufficient analgesia for laparoscopic pro¬cedure is important. A further studies must be done to confirm our findings.

Conclusion

The oral premedication of Vitamin C showed favorable results and reduces postoperative pain and consumption of fentanyl as rescue analgesic in postoperative period. It can be considered as part of multimodal analgesia.

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None.

Conflicts of interest

The authors declare no conflict of interest.

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