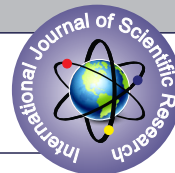


EFFECT OF VITAMIN-C PREMEDICATION ON POST-OPERATIVE ANALGESIC REQUIREMENT IN DIAGNOSTIC LAPAROSCOPIC GYNAECOLOGICAL SURGERIES UNDER GENERAL ANAESTHESIA: A RANDOMIZED CONTROLLED DOUBLE BLINDED INTERVENTIONAL STUDY



Anaesthesiology

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ABSTRACT

Introduction: Multimodal analgesia techniques are being increasingly used to manage post operative pain after laparoscopic surgeries. Objective of present study was to determine effect of vitamin C premedication on post operative analgesic requirement after diagnostic laparoscopic gynaecological surgeries.

Material And Methods: A Hospital based randomised controlled double Blinded interventional study was conducted at a referral tertiary care centre of Northern India from April 2018 to February 2019. A total of 90 subjects aged 20 – 40 years, ASA grade I and II, scheduled for elective Diagnostic Laparoscopic Gynaecological surgery were randomly to receive either oral solution of Vitamin-C or placebo. Postoperative vital parameters and VAS score and patient's satisfaction score were recorded.

Results: The VAS score was significantly lower in Vitamin C group from 30 to 120 minutes of post operative period. Requirement of analgesia was significantly less in Vitamin C group as compared to Placebo at 60 and 90 minutes. The post operative heart rate was significantly higher in placebo group at 60 and 90 minutes of post operative period. Patient satisfaction was significantly better in Vitamin C group at 6 hours and 12 hours post operative period. None of the patient experienced any side effects like bradycardia or hypertension.

Conclusion: Vitamin C can be considered as part of multimodal analgesia for such laparoscopic gynaecological surgeries with better patient satisfaction and no side effects.

KEYWORDS

Vitamin C, Ascorbic Acid, Laparoscopy, Analgesia

INTRODUCTION:

Diagnostic laparoscopy is an endoscopic procedure, performed to evaluate gynaecological complaints under general anaesthesia.^{1,2} Laparoscopic surgery can be associated with severe postoperative pain.^{3,4} Although most surgical patients receive some form of postoperative pain management, up to 75% of patients do not achieve adequate pain relief post-operatively.^{5,7} Effective postoperative pain management significantly improves patient satisfaction, reduces complications, and duration of hospital stay.⁸⁻¹¹

Various agents have been used to reduce postoperative pain. Opioids are widely chosen as analgesics for postoperative pain despite many possible adverse effects, such as nausea, vomiting, pruritus, and respiratory depression.¹² Many techniques have been proposed to reduce use of opioid such as preoperative, preventive or pre-emptive analgesia and multimodal analgesia techniques.^{13,14} Various studies have shown that Vitamin-C can be used as a component of multimodal analgesia to decrease requirement for opioid analgesics in surgical and cancer patients.^{10,15}

Vitamin-C has antioxidant, neuro-protective, and a neuro-modulating effect. It exerts its anti-nociceptive action through its antioxidant property by neutralizing the reactive oxygen species formed during the stress of surgery thus protecting cells and tissues from oxidative damage¹⁶⁻¹⁹. Also it has a role in modulating the sensitization of pain through its action on NMDA receptor.¹⁷

Because vitamin C is water soluble and easily excreted in the urine, supplementation with even high doses has little adverse effect when administered either orally or parenterally.²⁰ Overall, vitamin C appears to be a safe and effective adjunctive therapy for acute and chronic pain relief.¹⁵

Various studies are available for post operative analgesic properties of Vitamin C but very few studies are available for its analgesic role in Diagnostic Laparoscopic Gynaecological surgeries. So this study was designed to assess the effect of Vitamin-C premedication on post-operative analgesic requirement in Diagnostic Laparoscopic Gynaecological surgeries under General Anaesthesia.

MATERIAL AND METHODS:

A Hospital based randomised controlled double Blinded interventional study was conducted in Department of Anaesthesia, at a referral tertiary care centre of Northern India from April 2018 to February

2019. Sample size was calculated based on the Primary objective to determine any difference in mean VAS score during post operative period between vitamin C and placebo group. Sample size calculated was 45 in each group at 95% confidence and 80% power to verify the expected significant difference of 0.12 (± 0.20) in VAS score in both study groups at 4 hours post-operatively.

A total of 90 subjects aged 20 – 40 years, ASA grade I and II, scheduled for elective Diagnostic Laparoscopic Gynaecological surgery were recruited consecutively for the study and randomly allocated into two study groups using sealed envelope technique. Patients who had received anti inflammatory drug within 24 hours prior to surgery, patients with history of chronic pain or compromised airway or morbid obesity, those with history of convulsion, bleeding disorder or severe neurological deficit or chronic medical condition like hypertension, respiratory, cardiac, hepatic or renal disorder were excluded from the study. To ensure double blinding, study group (Group A) was given oral solution of Vitamin-C (1 gram) dissolved in 10 ml of water and control group was given 10 ml of same coloured glucose solution as placebo (Group B). The anaesthetist who gave the medication was different from the anaesthetist who took observation. All patients were subjected to standard pre anaesthetic check up and routine investigations using similar technique and protocol.

Patients were pre-medicated with inj. Ranitidine 50 mg i.v. inj. Metoclopramide 10 mg i.v. inj. Glycopyrrolate 0.004mg/kg i.v. inj. Midazolam 0.02mg/kg and inj. Fentanyl 2µg/kg. Patients were pre oxygenated for 3 minutes with 100% O₂. Anaesthesia was induced with Inj. Thiopentone Sodium 5-7 mg/kg and Inj. Succinyl choline 1-1.5mg/kg was used as muscle relaxant for intubation. Anaesthesia was maintained with Inj. Atracurium (0.5mg/kg loading dose + 0.1mg/kg as maintenance dose), oxygen, nitrous oxide and inhalation agent isoflurane (MAC 1-1.2). Monitoring was done throughout the procedure using continuous electrocardiography (lead II and V), heart rate, and non invasive blood pressure every 5 minutes, continuous pulse oximetry. After completion of surgery patients were reversed with inj. Neostigmine 0.05mg/kg and inj. Glycopyrrolate 0.008mg/kg. Patients were extubated after fulfilling standard extubation criteria and shifted to recovery room in stable condition. Postoperative vital parameters and VAS score (at 0, 30, 60, 90, 120, 180 and 240 minutes) and patient's satisfaction score were recorded using a pre designed semi structured proforma. Pain was recorded using VAS score on a range of 0 (no pain) to 10 (worst imaginable pain). Patient satisfaction

score was recorded on a scale of 1 (very satisfied), 2 (satisfied), 3 (neutral), 4 (dissatisfied) or 5 (very dissatisfied).

Written and informed consent was obtained from all subjects prior to inclusion into the study after complete explanation about the study protocol. Ethical clearance was obtained from institution ethics committee prior to initiation of study.

Statistical Analysis:

Quantitative variables were expressed as mean and standard deviation and were analyzed using unpaired t test while categorical / nominal variables were expressed as proportion and analyzed using chi square test. P value <0.05 was considered as statistically significant. All statistical analysis was done using SPSS version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA).

RESULTS:

A total of 45 subjects were included in the study with a mean age of 28.16 years in Group A and 27.29 years. Most of the subjects (80%) in both the group had ASA grade I (Table 1). No significant difference was seen in the intra operative mean arterial pressure and heart rate among the two groups (Figure 1 & 2). The VAS score was significantly lower in Group A at 30, 60, 90 minutes ($p<0.001$) and even at 120 minutes ($p=0.004$) indicating better pain relief with Vitamin C (Table 3). There was no analgesia requirement till 30 minutes in group A. At all time interval requirement of analgesia was less in group A as compared to group B, though significant difference was seen only at 60 and 90 minutes (Table 2).

The post operative heart rate was significantly higher in Group B at 60 minutes ($p=0.002$) and 90 minutes ($p=0.036$) of post operative period. For rest of the post operative period the Heart rate was similar in both groups (Figure 4). The post operative Mean arterial pressure was also significantly higher in Group B at 60 minutes ($p=0.003$) and 90 minutes ($p=0.040$) of post operative period. For rest of the post operative period the Mean arterial pressure was similar in both groups (Figure 5). Patient satisfaction was also significantly better in group A at 6 hours and 12 hours follow up (Table 3). None of the patient experienced any side effects like bradycardia or hypertension.

Table 1: Baseline Characteristics Of Study Subjects

	Group A	Group B	P value
Age (years)	28.16 $\pm$ 4.28	27.29 $\pm$ 3.88	0.317
Weight (Kg)	59.02 $\pm$ 9.73	58.44 $\pm$ 9.13	0.772
ASA Grade I	36 (80%)	36 (80%)	1.000
Grade II	9 (20%)	9 (20%)	

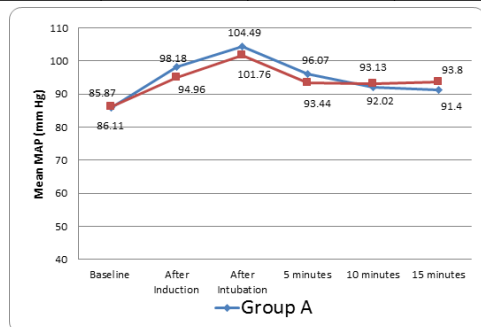


Figure 1: Intra Operative Mean Arterial Pressure

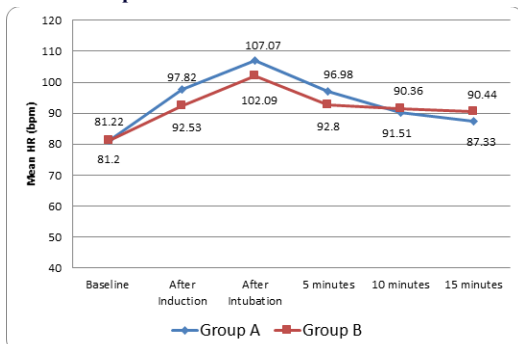


Figure 2: Intra Operative Heart Rate

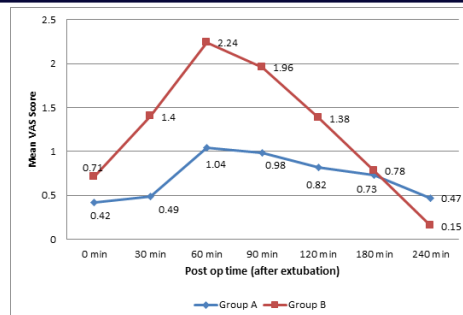


Figure 3: Mean Post Operative Vas Score

*0 minutes - just after extubation

Table 2: Proportion Of Study Subjects Requiring Analgesia During Post Op Period

	Group A	Group B	P value
0 minutes	0	2 (4.4%)	0.475
30 minutes	0	3 (6.7%)	0.240
60 minutes	10 (22.2%)	21 (46.7%)	0.027
90 minutes	5 (11.1%)	14 (31.1%)	0.039
120 minutes	2 (4.4%)	3 (6.7%)	1.000
180 minutes	4 (8.8%)	1 (2.2%)	0.357
240 minutes	1 (2.2%)	1 (2.2%)	1.000

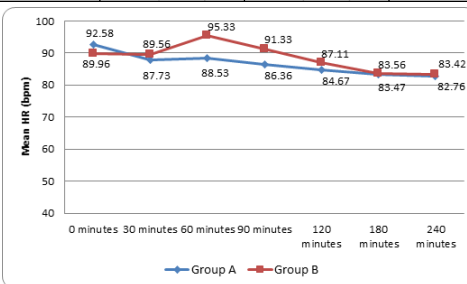


Figure 4: Post Operative Heart Rate

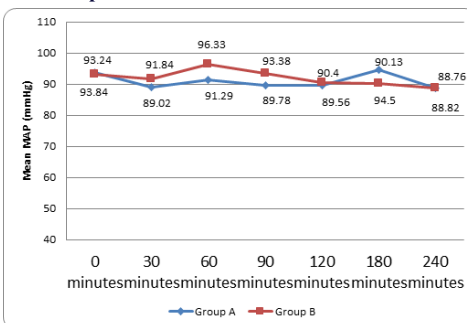


Figure 5: Post Operative Mean Arterial Pressure

Table 3: Distribution According To Patient Satisfaction Score

Follow up time	Group A	Group B	P value
6 hours post op	Score 1	2 (4.44%)	<0.001
	Score 2	28 (62.22%)	
	Score 3	15 (33.33%)	
	Score 4	0	
12 hours post op	Score 1	23 (51.1%)	<0.001
	Score 2	22 (48.9%)	
	Score 3	0	
	Score 4	7 (15.55%)	

DISCUSSION:

Laparoscopic procedures are associated with excessive postoperative pain that may delay recovery, increases hospital stay and patient's expenditure.^{5,7} Various groups of analgesic drugs like opioids provide adequate analgesia, but have many side effects like nausea, vomiting, constipation, pruritus and may cause respiratory depression.¹² Adjuvant antioxidant therapy like vitamin C have been used to decrease requirement of analgesics.^{5,12}

Demographic data was comparable in both the groups. It helped to

alleviate any confounding factor. No significant difference was seen in intra operative hemodynamic parameter between the two groups, which was consistent with findings of previous studies conducted by Kumar AA et al¹⁰, Ayatollahi V. et al²¹ and Laflı Tunay D et al²² who reported stable hemodynamic during intra operative period.

Postoperative MAP was comparable in both the groups at all time intervals except at 60 and 90 minutes where the mean MAP was significantly higher in Group A. Postoperative heart rate was also comparable at all time intervals except at 60 and 90 minutes where the mean heart rate was significantly lower in group A. Similar findings were reported by Kumar AA et al¹⁰. They also observed postoperative increase in hemodynamic parameters (MAP, HR) at 30 minutes, but in this study increase in hemodynamic parameters (MAP, HR) were observed at 60 and 90 minutes. This difference might be due to duration of surgery as diagnostic laparoscopy requires less time than laparoscopic cholecystectomy.

Contrary to this Sanja S Maric., et al²³ found no significant difference in the post operative vital parameters (MAP and HR) in their study (ketorolac + vitamin C group and ketorolac group). This might be because of use of ketorolac instead of placebo used in present study.

Mean VAS score was significantly less in group A (Vitamin C) as compared to group B (placebo) at 30, 60, 90 and 120 minutes in this study ($p < 0.05$). Kumar AA et al¹⁰ also reported decreased VAS score in immediate postoperative period in vitamin C group.

Ayatollahi V. et al²¹ and Laflı Tunay D et al²² also concluded that vitamin C significantly reduces the VAS score in postoperative period till 24 hours though in our study significant less VAS score was observed till 4 hours. This might be because of low dose of vitamin C (1 gram) used in our study as compared to 2 gram used in above mentioned studies. Sungho Moon et al²⁴ reported less pain scores in vitamin C group as compared to placebo group at 24 hour ($p < 0.001$) and 48 hour ($p = 0.035$) postoperatively. This difference in duration might be because of use of intravenous route of administration of vitamin C.

Requirement of analgesia was significantly less in group A at 60 minutes ($p = 0.027$) and 90 minutes ($p = 0.039$). Kumar AA et al¹⁰ also reported that vitamin C significantly reduced requirement of rescue analgesia in post operative period 0 minute and 30 minutes. Study done by Sanja S Maric., et al²³ also supports findings of present study.

Vitamin C is thought to exert its anti-nociceptive effect through its antioxidant action, neutralizing the reactive oxygen species formed during the stress of surgery, that have a major role in development of postoperative pain.^{10,16-20} Vitamin C also modulates neurotransmitters binding to NMDA receptors such as glutamate, involved in pain sensitization.¹⁷ Acute inflammation induced by tissue damage causes release of reactive oxygen species.

Patient's Satisfaction was also significantly better in Group A at 6 hours and 12 hours as evaluated us patient satisfaction score. This finding is supported by study done by Jeon Y et al¹⁹. Jeon Y et al¹⁹ reported postoperative pain scores at rest, 2, 6, and 24 hours were significantly lower in the vitamin C group. None of the patient experienced any side effects in present study.

CONCLUSION:

The oral premedication of Vitamin C decreases VAS score and reduces consumption of analgesic requirement in post operative period; it significantly lowers the pain intensity and also improves patient satisfaction score. It can be considered as part of multimodal analgesia. However, further studies are required to find out the dose and route of administration to establish optimum dose regimen and route.

Conflict Of Interest: Nil

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