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Original Article

Anaesthesia Section

Effect of Intravenous Vitamin C and N-acetylcysteine on Postoperative Pain and Opioid Consumption after Laparoscopic Gynaecologic Oncosurgeries: A Randomised Controlled Study

ND RACHANA[1], NAMRATA RANGANATH[2], VR PALLAVI[3], GS SHASHIDHAR[4], BH ARATHI[5], VB GOWDA[6]

ABSTRACT

Introduction: Postoperative pain is one of the common causes of increased postoperative morbidity and delayed recovery. Pain causes adverse effects such as hypertension, tachycardia, myocardial ischaemia, decreased alveolar ventilation, poor wound healing, and postoperative morbidity. Vitamin C and N-acetylcysteine (NAC), which is a novel co-analgesic, are being studied to reduce postoperative pain and opioid consumption.

Aim: To study the effect of intravenous Vitamin C and NAC on postoperative surgical pain and opioid consumption after laparoscopic gynaecologic oncosurgeries.

Materials and Methods: The present study was a randomised controlled study conducted at the Department of Anaesthesiology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India on 300 patients of American Society of Anaesthesiologists (ASA) physical status 1 and 2 scheduled for laparoscopic Gynaeconcology surgery after obtaining written informed consent. All the selected patients were randomly allocated into three groups. Group P was the control group in Group N patients received intravenous injections of NAC (50 mg/kg) and vitamin C infusion (50 mg/kg) in Group C. Patients were explained about the visual analogue pain scale preoperatively. In the postoperative period, VAS scores were recorded and noted along with the rescue analgesics received and side-effects.

Results: Haemodynamic variables were comparable among all three groups. The number of patients who had VAS scores of more than 4 was lower in group C (Vitamin C) at various time intervals when compared to the NAC and placebo groups. It was also statistically significant at 45 minutes, 60 minutes, 90 minutes, 150 minutes, 180 minutes, 300 minutes, and 10 hours (p-value=0.014, <0.001, <0.001, <0.001, 0.003, 0.005, 0.006, respectively). Postoperative opioid consumption was significantly reduced in group C (Vitamin C) compared to the other two groups (p-value <0.001).

Conclusion: Intraoperative Vitamin C usage reduced postoperative pain and fentanyl consumption in the postoperative period, and NAC can be used as a part of multimodal analgesia.

Keywords: Analgesia, Co-analgesics, Fentanyl, Pain scores

INTRODUCTION

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. Adequate pain control in cancer patients undergoing surgical procedures remains the primary goal of anaesthesiologists. Inadequate postoperative analgesia can lead to delayed recovery, mobility issues, delay in initiating chemotherapy, pneumonia, myocardial infarction, and depression. This can further increase morbidity and mortality in cancer patients, contributing to a diminished quality of life [2].

The goal of adequate postoperative pain control is best achieved through multimodal and preemptive analgesia. Postsurgery pain is mainly an inflammatory nociceptive kind of pain related to noxious stimuli, resulting in the perception of pain. It could also result from the release of chemical mediators due to tissue inflammation [3]. In postoperative pain management, opioids are one of the most widely used classes of analgesics as part of multimodal analgesia. The use of opioids can be associated with Postoperative Nausea and Vomiting (PONV), sedation, respiratory depression, and delayed recovery in the postsurgical period. Additionally, some patients are known to develop an addiction to opioids with long-term use. Recently, non opioid analgesic modalities and alternatives have been introduced to enhance pain management and reduce the consumption of opioids and opioid-related side-effects in the postoperative period [3]. Among the various available co-analgesics, Vitamin C and NAC have also been studied.

Vitamin C (ascorbic acid) is a water-soluble vitamin that has antioxidant, neuromodulating, and neuroprotective effects [4,5]. Additionally, vitamin C has been shown to modulate pain sensitisation through its action on the N-methyl-D-aspartate (NMDA) receptor. Recent studies have indicated that vitamin C supplementation can be useful as an adjunct to pain management by reducing opioid consumption and side-effects related to opioids [6-8].

Analgesic drugs currently under trial target group-II metabotropic glutamate receptor subtypes (mGlu2 and mGlu3 receptors) [9,10]. NAC is a novel co-analgesic under trial for its analgesic properties. It acts by activating the glutamate: cystine antiporter (Sxc) and thus reinforcing the endogenous activation of mGlu2/3 receptors [11]. In animal models, it has been shown to have analgesic effects on neuropathic and inflammatory pain types, thereby reducing opioid consumption and related side-effects [12,13]. NAC is known to regulate oxidative stress, reduce reactive oxygen species release, and has been used in treating complex pain syndromes, as chronic pain states often have excessive levels of reactive oxygen species [14,15]. NAC has shown positive effects on chronic neuropathic pain, but no studies have been conducted on acute pain conditions [15]. Due to its easy availability and cost-effectiveness, NAC can

be used as an adjunct to opioids in an attempt to reduce opioid consumption.

Therefore, aim was to study the effects of high-dose vitamin C (50 mg/kg) and the novel co-analgesic NAC on postoperative opioid consumption in patients undergoing laparoscopic gynaecological oncosurgeries during the first 24 hours after surgery as the primary objective. The secondary objectives included studying pain scores in all three groups and postoperative side-effects. This was the first study of its kind to assess the safety and efficacy of perioperative administration of Vitamin C and NAC for postoperative surgical pain relief and opioid consumption in laparoscopic gynaeco-onco surgeries.

MATERIALS AND METHODS

This prospective non blinded randomised controlled study was conducted between January 2019 and December 2022. Approval for the study was obtained from the ethical committee of Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India Institutional Ethical Committee (IEC) number (KMIO/MEC/2018/02/C/AN/35). The study was registered under CTRI with the CTRI No – CTRI/2019/09/021332.

Inclusion criteria: All patients aged 18 to 75 years undergoing elective laparoscopic gynaecological oncology procedures under general anaesthesia were enrolled in the study.

Exclusion criteria: Patients with a history of allergy to systemic opioids, chronic opioid use, substance use disorder, sleep apnoea, coagulopathy, and analgesic use within 24 hours were excluded from the study.

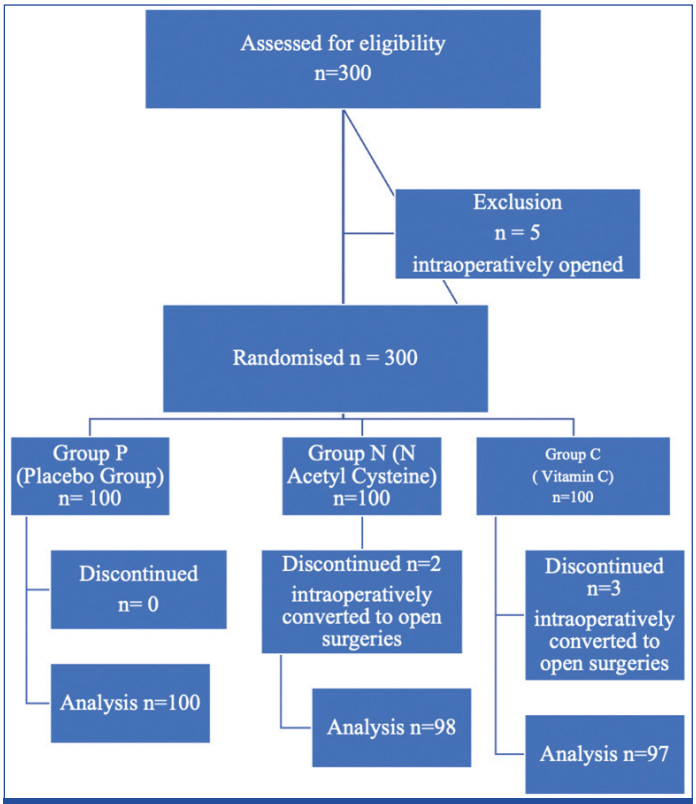
A member of the research team contacted the patients to explain the study protocol and obtain written informed consent for participation. The day before surgery, all patients were provided with information on how to rate pain intensity on the Numeric Rating Scale (NRS), with 0 indicating no pain and 10 indicating the worst pain imaginable. Patients were randomly allocated to groups based on the randomisation table.

Sample size calculation: A sample size of 300 (100 cases in each group) was deemed adequate, considering 80% power and a 5% alpha level of significance.

Methodology: General anaesthesia was administered according to a standard protocol and monitored in accordance with the American Society of Anaesthesiologists guidelines [16]. Anaesthesia was induced with intravenous midazolam 1 mg, fentanyl 1 µg/kg, propofol (1 to 2 mg/kg), and vecuronium (0.1 mg/kg) to facilitate intubation. After anaesthesia induction and creation of pneumoperitoneum at a flow rate of 12 to 14 mL per minute with intraperitoneal pressures ranging from 12 to 14 mm Hg, the prepared injection was administered by a team member based on group allocation. Patients in the Vitamin C group (group C) received vitamin C 50 mg/kg [17] (ascorbic acid 10 g/20 mL), those in the NAC group (group N) received NAC 50 mg/kg [18]. Both drugs were administered as an infusion mixed with normal saline for a total injection volume of 50 mL, and normal saline 50 mL was infused to the placebo group (Group P) of patients. The prepared solution was infused over 30 minutes using an infusion pump once the pneumoperitoneum was created. Doses of Vitamin C and NAC were adjusted from the doses mentioned in CTRI accordingly after the pilot study. Anaesthesia was maintained using 1-1.5% isoflurane in a mixture of 50% oxygen in air. Vecuronium was utilised to maintain adequate muscle relaxation, i.v. injection of fentanyl 25 µg bolus was used as intraoperative analgesia, and intravenous lactated Ringer's solution was administered at a rate of 4 to 5 mL/kg/h during surgery as maintenance fluid. Ondansetron 4 mg intravenously was administered to prevent PONV unless contraindicated. All surgeries were performed with a mini-laparotomy incision below the umbilicus at the camera port using a 4-port technique with patients in the Trendelenburg position.

After completion of surgery and meeting extubation criteria, neuromuscular blockade was reversed using Neostigmine and Glycopyrrolate. Extubated patients were transferred to the postoperative care unit. Upon arrival at the postoperative care unit, patients were evaluated for pain using a Visual Analog Scale (VAS) score. If the pain intensity exceeded a VAS score of 4 for ≥30 minutes, rescue analgesia (Inj. fentanyl 25 µg) was administered.

A research assistant was assigned to monitor patients' postoperative surgical pain scores, PONV, fentanyl consumption, side-effects, and the need for rescue analgesia every 15 minutes during their stay in the PACU for the first hour, and every 30 minutes until four hours postsurgery, and then at 6, 8, 10, 12, 14, 16, 18, 20, and 24 hours after surgery. A total of 300 patients were enrolled in the study with written informed consent. Five patients were excluded from the study as laparoscopy was converted to open laparotomy intraoperatively [Table/Fig-1].



[Table/Fig-1]: CONSORT flowchart.

STATISTICAL ANALYSIS

The collected data was entered into the Microsoft Excel program. Univariate and multivariate frequency tables were generated using Statistical Package for the Social Sciences (SPSS) statistical software. A comparison of parameters between cases and controls, measured on a continuous scale, was conducted using the Independent Student's t-test. For categorical variables, an association study was performed using the Mantel-Haenszel Chi-square test. A p-value of <0.05 was considered statistically significant.

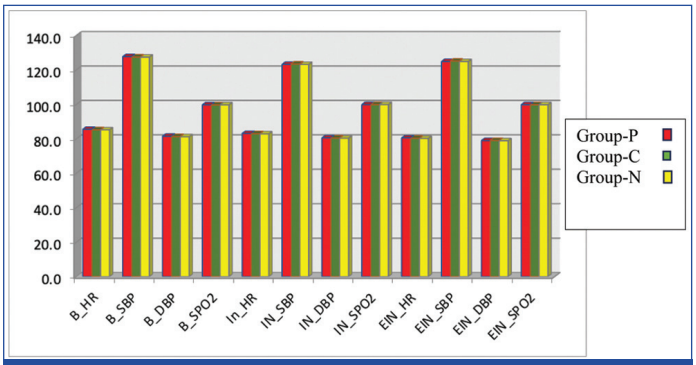
RESULTS

Demographic details were similar among all three study groups and was not significant statistically [Table/Fig-2].

Parameters	Group P	Group C	Group N
Age (years)	62.94±14.83	65.75±13.97	63.56±14.27
Weight (kg)	49.8±8.09	51.5±7.91	50.3±8.07

[Table/Fig-2]: Demographic details.

Haemodynamic variables noted at the baseline (B) at the beginning of infusion (IN) and at the End of Infusion (EIN) showed no difference between all three groups [Table/Fig-3].



[Table/Fig-3]: Haemodynamic variables.
B: Baseline; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SpO_2: Saturated oxygen; IN: Beginning of infusion; EIN: End of infusion

Postoperative pain scores in the three groups at various time intervals are presented in [Table/Fig-4]. Mean pain scores, when compared between the three groups, demonstrated that group C (Vitamin C group) had more consistent and lower pain scores compared to the other two groups.

	Group P	Group N	Group C
On arrival	1.85 (1.45)	1.89 (1.62)	2.02 (1.33)
5 mins	1.91 (1.25)	1.19 (1.25)	1.96 (1.18)
15 mins	2.16 (1.19)	2.25 (1.30)	2 (0.97)
30 mins	2.35 (1.14)	2.26 (1.11)	2.02 (0.84)
45 mins	2.18 (0.93)	2.04 (0.94)	1.92 (0.75)
60 mins	2.47 (0.92)	2.44 (1.09)	2.02 (0.730
90 mins	2.62 (1.13)	2.68 (1.41)	2.07 (0.70)
120 mins	2.55 (1.01)	2.43 (1.11)	2.32 (0.98)
150 mins	2.67 (0.11)	2.49 (1.05)	2.22 (0.86)
180 mins	2.55 (1.10)	2.37 (1.08)	2.10 (0.85)
210 mins	2.35 (0.98)	2.36 (1.22)	2.13 (0.75)
240 mins	2.45 (1.34)	2.15 (1.28)	2.34 (1.24)
270 mins	2.42 (0.88)	2.35 (0.97)	2.28 (0.97)
300 mins	2.91 (1.21)	2.65 (1.16)	2.37 (0.98)
8 hrs	2.20 (0.99)	2.1 (0.92)	2.11 (1.03)
10 hrs	2.57 (1.35)	2.55 (1.54)	2.07 (0.99)
12 hrs	2.35 (1.11)	2.09 (0.78)	2.18 (1.01)
14 hrs	2.3 (1.1)	2.17 (1.16)	1.91 (0.82)
16 hrs	2.11 (0.91)	197 (0.83)	1.78 (0.83)
20 hrs	1.85 (0.84)	1.81 (0.83)	1.54 (0.78)
24 hrs	1.77 (1.02)	1.64 (0.88)	1.57 (1.04)

[Table/Fig-4]: Mean average pain scores between three groups.

The VAS score was assessed for 24 hours postsurgery. In this study, the number of patients with VAS scores exceeding four was lower in group C (Vitamin C) at various time intervals compared to the NAC and placebo groups. The differences were statistically significant at 45 minutes, 60 minutes, 90 minutes, 150 minutes, 180 minutes, 300 minutes, and 10 hours (p-value=0.014, <0.001, <0.001, <0.001, 0.003, 0.005, 0.006 respectively) [Table/Fig-5].

Postoperative opioid consumption was significantly reduced in group C (vitamin C) as compared to the other two groups with a p-value of <0.001 [Table/Fig-6].

A total of 31 patients in group C, 49 in group N, and 58 patients in group P received rescue analgesics. A significantly lower number of patients in the Vitamin C group received rescue analgesics (p-value=0.0013) [Table/Fig-7].

Group	Number of patients who had pain scores more than 4			p-value
	Placebo	N acetyl cysteine	Vitamin C	
On arrival	34	37	30	0.545
5 mins	29	33	30	0.787
15 mins	28	31	18	0.082
30 mins	34	29	20	0.080
45 mins	26	20	10	0.014
60 mins	44	42	18	<0.001
90 mins	46	48	21	<0.001
120 mins	44	40	28	0.057
150 mins	57	52	30	<0.001
180 mins	40	40	20	0.003
210 mins	35	33	25	0.285
240 mins	29	19	28	0.210
270 mins	36	32	30	0.686
300 mins	58	49	35	0.005
8 hrs	30	25	23	0.537
10 hrs	49	42	27	0.006
12 hrs	27	17	20	0.224
14 hrs	33	25	15	0.013
16 hrs	33	22	17	0.035
20 hrs	23	20	9	0.024
22 hrs	14	13	7	0.247
24 hrs	14	13	13	0.979

[Table/Fig-5]: Pain scores of more than four between three groups.

Group	N	Mean±SD (Fentanyl in µg)	p-value
P (Placebo)	100	54.70±38.683	<0.001
N (N acetyl cysteine)	98	56.89±41.521	
C (Vitamin C)	97	27.53±27.803	
Total	295	46.52±38.768	

[Table/Fig-6]: Total postoperative opioid consumption.

Group			p-value
P (Placebo)	N (N acetyl cysteine)	C (Vitamin C)	
58	49	31	0.0013
(58%)	(50%)	(32%)	

[Table/Fig-7]: Number of patients receiving rescue analgesics.
One-way ANOVA test

In this study, minimal side-effects were observed in group C compared to the other two groups. In the control group, 10% of patients experienced vomiting, and 10% experienced drowsiness compared to the other groups. None of the patients in any group experienced respiratory depression [Table/Fig-8].

Group	Vomiting	Drowsiness
Group C	5 (5.1%)	5 (5.1%)
Group P	10 (10%)	5 (5%)
Group N	20 (20.4%)	10 (10.2%)

[Table/Fig-8]: Postoperative side-effects.

DISCUSSION

In this study, a significant reduction in opioid consumption and postoperative pain was observed in the Vitamin C group. Jeon Y et al., conducted a randomised controlled trial on the effect of using intravenous high-dose vitamin C on postoperative pain and morphine consumption after laparoscopic colectomy. Their study showed that postoperative pain at rest during the first 24 hours and morphine consumption during the first two hours were reduced after laparoscopic colectomy. However, no difference was noted in

the consumption of morphine between the treatment and control groups at six hours and 24 hours. High-dose vitamin C infusion also decreased the frequency of demand for rescue analgesics [17]. Similarly, in this study, there were decreased postoperative pain scores and reduced cumulative opioid consumption in the group of patients who received Vitamin C.

Wilson SH et al., conducted a randomised pilot trial on the impact of intraoperative NAC on opioid consumption following spine surgery. They used NAC in doses of 50, 100, and 150 mg/kg, and recorded opioid consumption, pain scores, and time to opioid rescue. The study found that patients who received NAC had lower consumption of postoperative opioids and pain scores. These results were comparable to the present study, showing a slight reduction in opioid consumption and pain scores, though not statistically significant [18].

Hung KC et al., conducted a meta-analysis of randomised controlled trials on the effect of perioperative Vitamin C on postoperative analgesic consumption. Their results demonstrated significant postoperative reductions in the requirement for opioids and a decrease in pain severity in patients receiving perioperative vitamin C. This suggests that vitamin C may be beneficial as part of a multimodal approach to postoperative analgesia in surgical patients [19]. These findings were consistent with the results of the current study.

Mulkens CE et al., conducted a randomised controlled clinical trial on postoperative pain reduction by pre-emptive NAC. They concluded that there were no differences in pain scores postoperatively between the placebo group and the NAC group. However, the percentage of bothersome side-effects in the NAC group was high, leading them to not recommend the preemptive intravenous use of NAC to reduce postoperative pain in patients undergoing laparoscopic inguinal hernia repair [20]. In the present study, the NAC group of patients had slightly lower pain scores compared to the control group, but the difference was not statistically significant. The incidence of side-effects related to NAC in present study was also not significant.

Gorpynchenko I et al., conducted an observational comparative cohort study on the patients with chronic prostatitis and chronic pelvic pain syndrome, oral NAC (600 mg) daily over one month resulted in a 25% decrease in pain scores. This study suggests that NAC has anti-inflammatory effects and helps in reducing pain [21].

Seyfi S et al., conducted a randomised controlled study on NAC's effect on postoperative pain after laparoscopic cholecystectomy. The study concluded that NAC can inhibit the function of lipoproteins and prostaglandins due to its anti-inflammatory properties. It was found that reduced glutathione peroxidase and dismutase were restored, indicating that NAC can be used to treat pain or reduce analgesic doses [15]. However, in this study, there was no significant decrease in pain scores in the NAC group compared to the other two groups. Li J et al., suggested that NAC attenuates neuropathic pain by suppressing matrix metalloproteinases [22].

Suter M et al., conducted a study on Vitamin C perioperatively in patients undergoing non cardiac surgery. A systematic review and meta-analysis of randomised trials revealed a small reduction in postoperative pain in patients who received Vitamin C. This finding was similar to the reduction in postoperative pain observed in patients receiving Vitamin C in the current study [23].

Limitation(s)

There was no consensus on the dosing of NAC.

CONCLUSION(S)

There was a significant reduction in opioid consumption and pain scores in the postoperative period in the Vitamin C group compared to the NAC and control groups of patients. The NAC group of patients also experienced reduced opioid consumption and pain scores, but this was not statistically significant. Therefore, Vitamin C can be used as part of multimodal analgesia for acute postoperative pain, with the additional benefit of reducing opioid consumption and its associated side-effects. NAC as a co-analgesic for pain needs further evaluation regarding dosing and efficacy.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Anaesthesiology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India.
2. Professor, Department of Anaesthesiology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India.
3. Professor, Department of Gynaeconcology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India.
4. Associate Professor, Department of Anaesthesiology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India.
5. Professor and Head, Department of Anaesthesiology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India.
6. Professor and Ex-Head, Department of Anaesthesiology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. GS Shashidhar,
Kidwai Cancer Institute, Dr. MH Marigowda Road, Near Dairy Circle,
Bengaluru-560029, Karnataka, India.
E-mail: rachanakiran84@gmail.com

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