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ORIGINAL RESEARCH **GENERAL ANESTHESIA**

Analgesic effect of preoperative melatonin and vitamin C administration, alone or in combination, in major abdominal surgery; a randomized controlled study

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ABSTRACT

Background & objectives: Several studies have shown that melatonin and vitamin C used as an analgesic adjuvant, can spare opioid use, resulting in a better analgesic profile with fewer adverse effects and shorter hospital stay. However, we found no studies which might have investigated the impact of a combination of both. We compared the effect of melatonin, vitamin C, and their combination on postoperative opioid consumption.

Methodology: Sixty patients scheduled for major abdominal surgeries were randomly allocated into three equal groups with 20 patients in each; melatonin group (Group M), vitamin C (Group C), and combined melatonin and vitamin C (Group CM). Two hours before surgery, all patients received the study medications orally, which was continued for 3 days postoperative at the same time of the first administration; Group M received 10 mg of melatonin, Group C received 1 gm of vitamin C, and Group MV received both melatonin (10 mg) and vitamin C (1 gm). The primary outcome was the total morphine consumption in 24 hours postoperatively, with patients' pain scores as measured by Numeric Pain Rating Scale (NPRS), the incidence of postoperative nausea and vomiting (PONV), and postoperative chronic pain as secondary outcomes.

Results: Postoperative morphine consumption (in the first 24 hours) was significantly lower in Group CM (16.7 ± 2.4 mg) than in Group M (20.98 ± 1.38 mg), and Group C (24.36 ± 3.12 mg) ($P < 0.001$). Group CM showed lower pain scores, decreased incidence of PONV, and a longer time to first request for analgesics. However, lower sedation scores were observed. There was no statistical difference among all groups regarding post-operative chronic pain incidence.

Conclusion: Combined use of melatonin and vitamin C in patients undergoing major abdominal surgery with mid-line incision provides a synergistic analgesic effect for the postoperative pain management with lower postoperative pain scores, less opioid consumption, and lower incidence of PONV compared to the use of any one of these.

Abbreviations: CPSP: Chronic Post-Surgical Pain, NPRS: Numeric Pain Rating Scale, PONV: postoperative nausea and vomiting, TAHBSO: Total Abdominal Hysterectomy with Bilateral Salpingo-Oophorectomy

Keywords: Melatonin; major abdominal surgery; Numeric Pain Rating Scale; opioid consumption; postoperative pain; PONV; vitamin C.

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1. INTRODUCTION

Major abdominal surgeries cause changes in neuro-hormonal response, resulting in postoperative pain, various organ dysfunction, and prolonged hospitalization. Inadequate pain relief after major abdominal surgeries adversely affects the surgical outcome through slower rehabilitation and a more extended hospital stay.[1]

Chronic Post-Surgical Pain (CPSP) is defined as a persistent pain of duration longer than 2 months after the surgical procedure, excluding other causes of pain such as malignancy, infection, and pre-existing pain problems. Many procedures are likely to be associated with CPSP if the postoperative pain is not adequately controlled.

Major abdominal surgeries in previous studies have reported CPSP with an incidence ranging from 17% to 32%.[2]

Post-operative pain after major abdominal surgery is usually controlled through multimodal analgesia, which may be in the form of intravenous opioids, non-steroidal anti-inflammatory drugs, and paracetamol, together with regional blocks.[3]

There are many side effects of opioids, including sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression.[4]

Therefore, many studies have been conducted to achieve effective postoperative pain control and improve patient satisfaction with minimal hazards. Several studies showed that the use of different adjuvants could spare opioid use, resulting in better rehabilitation, surgical outcomes, and less hospital stay.[5]

One of these adjuvants is melatonin. Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone the pineal gland produces and is essential to the circadian rhythm. Melatonin has proved to have a postoperative analgesic effect and to reduce opioid consumption. Administration of melatonin has dose-dependent long- term anti-nociceptive effects in acute, neuropathic, and inflammatory pain.[6]

Vitamin C is a water-soluble vitamin responsible for normal growth and development. It also has antioxidant, neuro-protective, and neuro-modulation effects. Vitamin C has been proven to reduce acute pain and the prevalence of complex regional pain syndromes with its anti-nociceptive effect.[7] Certain studies have demonstrated that the combination of vitamin C with an opioid may diminish both opioid consumption for pain relief and the rate of opioid-related adverse effects.[8]

Several multimodal approaches have been advocated to reduce opioid consumption by using either melatonin or vitamin C.[9] This is the first study conducted on using the combination of both in reducing opioid consumption in major abdominal surgeries.

2. METHODOLOGY

This randomized, double-blinded, controlled study was conducted in the general surgery, uro-surgery, and gynecology operating rooms of Kasr Al Ainy Hospital, Cairo, Egypt, from January 2023 to July 2024. Ethical approval of the Institutional Ethics Committee (No. MD-15-2022) was obtained according to the ethical standards of the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (No. NCT06374771).

We enrolled 60 patients aged between 18 and 60 y, ASA- I–II, and scheduled for major abdominal surgeries with mid-line incisions, e.g., radical prostatectomy, nephrectomy, Total Abdominal Hysterectomy with Bilateral Salpingo-Oophorectomy (TAHBSO), hepatectomy, splenectomy, hepatic hydatid cyst excision. Informed signed consent was obtained from every participant. Those who refused to participate, were known allergic to the drugs used in the study, had a hepatic failure (Child class B- Child class C) or a renal impairment (creatinine >2mg/dL or chronic kidney disease on regular dialysis), or had a history of psychiatric or mental disorders, Chronic pain syndromes (neuropathic pain, post-herpetic neuralgia, Complex regional pain syndrome), or drug or alcohol abuse, were excluded.

Randomization was performed using computer-generated numbers with Random Allocation Software (https://random-allocation-software.software.informer.com/2.0/) ina 1:1:1 ratio. Sixty consequentially numbered opaque envelopes (twenty per group) containing group assignment and drug administration instructions were made. A research assistant was responsible for opening the envelopes and administering the assigned drug with no further involvement in the study. A blinded anesthesiologist was responsible for the anesthetic

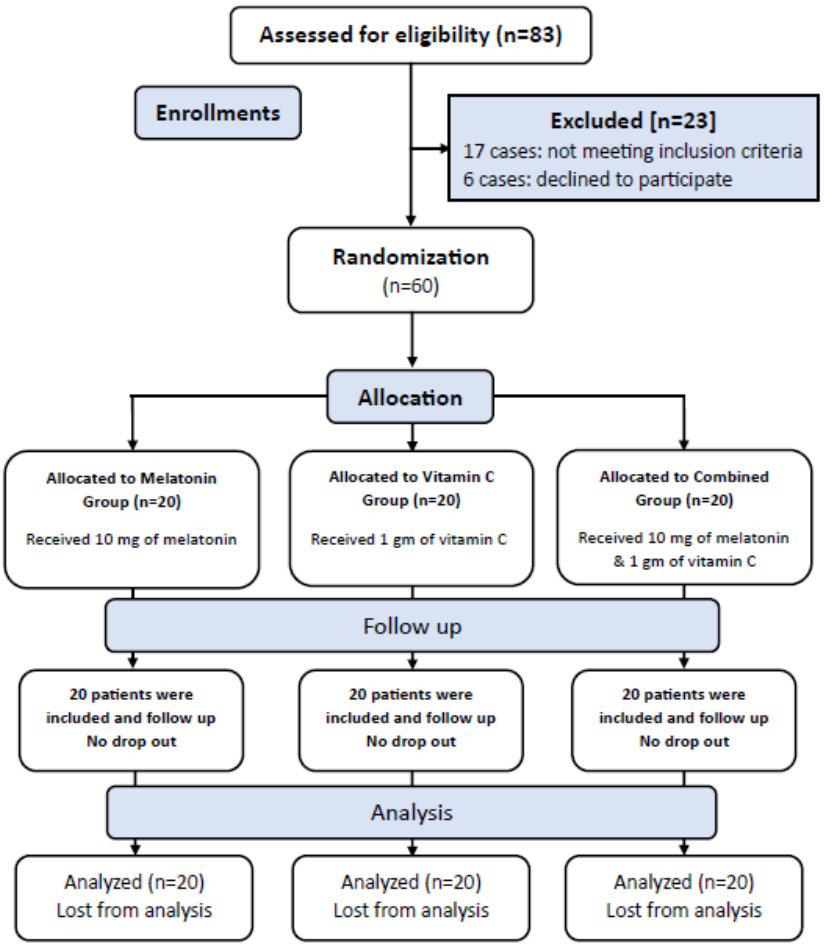

Figure 1: CONSORT flow diagram of the enrolled patients.

management, perioperative data collection, postoperative pain assessment, and analgesia administration.

Patients were allocated into three groups: the melatonin group (Group M), the vitamin C group (Group C), and the Melatonin and vitamin C group (Group CM).

The primary outcome was the total morphine consumption in the first 24 postoperative hours. Other outcomes included intraoperative fentanyl consumption, intraoperative and postoperative blood pressure (BP) and heart rate (HR), postoperative Richmond Agitation Sedation Scale (RASS), the time to first analgesic requirement, defined as the first recognized time point of Numeric Rating Scale (NRS) > 4 assessed during the first 24 h, the number of morphine boluses given after discharge from PACU, the frequency of postoperative chronic pain, and any adverse events.

2.1. Management Protocol

The day before surgery, participants were evaluated by acquiring a thorough medical history, physical examination, and investigations. Two hours before surgery, all patients will receive the study drugs orally: 10mg of melatonin for Group M (Melatonin 10 mg - Puritan's Pride premium company), 1 gm of vitamin C for Group C (Sanso C 1000 mg - AUG pharma company), and 10mg of melatonin and 1 gm of vitamin C for Group CM.

The patients were transferred to the preparation room one hour before the procedure, and the NRS pain score was explained to all candidates (zero corresponds to no pain, and 10 indicates the worst unbearable pain). Baseline vital signs were recorded, including noninvasive measuring of systolic, mean, diastolic arterial blood pressures, heart rate, and oxygen saturation.

2.2. Anesthetic technique

Standard monitoring (non-invasive blood pressure, electrocardiography, and pulse oximetry) was applied upon arrival at the operating room. The patient received pre-induction ondansetron 8mg. Following pre-oxygenation via a face mask for 3 min, anesthesia was induced using propofol 1-2 mg/kg and fentanyl 2 µg/kg. Atracurium 0.5 mg/kg was administered to facilitate endotracheal intubation. After intubation, the capnography will be connected, and the patients will be mechanically ventilated to maintain end-tidal CO_2 between 30-35 mmHg.

Anaesthesia was maintained with sevoflurane in 50% oxygen, and atracurium 0.1mg/kg every 20 min was administered to maintain muscle relaxation. After the skin incision, a bolus dose of morphine 100 mcg/kg was given. Fentanyl at 1µg/kg was administered as rescue analgesia if an intraoperative increase in heart rate or systolic blood pressure by 20% occurred after the exclusion of other causes rather than pain. Before skin closure, paracetamol 1gm was given intravenously. A bispectral index monitoring device was used to monitor the anesthesia depth. Readings within 40 to 55 were targeted throughout the procedure. Mean blood pressure and heart rate were maintained within ±20%.

2.3. Postoperative Management

Recovery time was recorded, defined as the time from extubation to the time of achieving Aldrete scores ≥ 9. The patient was transferred to the post-anesthesia care unit (PACU); Blood pressure, heart rate, and oxygen saturation were monitored every 15 min till discharge from the PACU. In PACU, 50mcg/kg of morphine was given by the physician to all patients. Then, all patients received a continuous morphine infusion of 5mcg/kg/hour through a disposable infusion pump 275ml with a constant flow of 5ml/hour (Zhejiang Fert Medical Device Co., Ltd). The patients were instructed to report any pain to a pain nurse, and if the NRS increased to more than 4, the pain nurse informed the anesthesiologist. Inadequate analgesia (NRS >4) was treated with a clinician bolus of 50mcg/kg with a time interval of 30 min at least between the additional doses till NRS decreased to less than 4. Excessive drowsiness or respiratory depression was treated by stopping the pump until appropriate recovery and by a decrease in the demand dose of 20%. 1 gm of paracetamol was administered intravenously every 8 hours. Postoperative hemodynamics, including systolic and diastolic blood pressures (SBP and DBP), HR, arterial oxygen saturation, NRS, and RASS, were recorded at 2, 4, 6, 12, and 24 hours. The total morphine consumption, including the continuous infusion, total boluses required, and the number of boluses, were recorded at the end of the first 24 hours. The side effects of opioids were recorded, e.g., postoperative nausea and vomiting (PONV), pruritus, urine retention, and allergic reactions. Vomiting was treated with metoclopramide 10 mg. Ondansetron 8mg was given in persistent vomiting. Respiratory depression was treated with 1 mcg/kg of naloxone and oxygen supplied by an oxygen mask. NRS and patient satisfaction were recorded from the patient after 48, 72, 96 h, one month, and 3 months post-operative.

A blinded physician conducted CPSP assessments during patients' visits to the pain clinic in the first and third postoperative months. They included the location, intensity, nature, duration of pain, and any aggravating or mitigating factors besides the used analgesic medication. CPSP was assessed using the Numeric Pain Rating Scale.

2.4. Statistical analysis

Using the G*power 3.1.9.2 program (Universitat Kiel, Germany) based on data from a previous study (10), a total sample of 54 (18 per group) subjects achieves 85% power to detect a difference of at least 5.5 mg in 24 h morphine consumption at an alpha error of 0.05. The common standard deviation is assumed to be 7. The number of envelopes will be increased to 60 (20 per group) to compensate for possible dropouts.

The Statistical Package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Categorical measurements were expressed as numbers and percentages (n [%]), and numerical measurements were expressed as mean (95% confidence intervals

Table 1: Comparative demographic data and baseline characteristics

Parameter		Melatonin group (n = 20)	Vitamin C group (n = 20)	Melatonin + Vit C group (n = 20)	P-value
Age (yr)		49.0 ± 12.1	44.2 ± 14.2	44.8 ± 11.3	0.43
Weight (kg)		82.6 ± 12.1	84 ± 13.6	84.2 ± 13.4	0.91
Operative time (hr)		2.6 ± 0.6	2.5 ± 0.6	2.4 ± 0.7	0.69
Recovery time (hr)		5.2 ± 1.88	4.6 ± 1.67	5.6 ± 2.01	0.239
Gender	Male	6 (30)	8 (40)	8 (40)	0.75
	Female	14 (70)	12 (60)	12 (60)	
ASA	I	9 (45)	9 (45)	11 (55)	0.76
	II	11 (55)	11 (55)	9 (45)	
	Partial hepatectomy	3 (15)	2 (10)	3 (15)	
	Hepatic hydatid cyst excision	2 (10)	2 (10)	3 (15)	
	TAHBSO	8 (40)	7 (35)	5 (25)	
	Radical prostatectomy	5 (25)	6 (30)	6 (30)	
Surgery	Nephrectomy	2 (10)	3 (15)	3 (15)	0.82

ASA= American Society of Anesthesiologists, TAHBSO: Total Abdominal Hysterectomy with Bilateral Salpingo-Oophorectomy.
Data are presented as mean ± SD or numbers (%)

Table 2: Comparative analgesics consumption and PONV in the three groups

Variables	Melatonin group (n = 20)	Vitamin C group (n = 20)	Melatonin + Vit C group (n = 20)	P-value
Postop morphine consumption (mg)	20.98 ± 1.38 +‡	24.36 ± 3.12 *	16.7 ± 2.4	0.001
Fentanyl consumption (µg)	169.6 ± 47.5 ‡	207.0 ± 39.2 *	156 ± 30.3	0.001
First time to rescue analgesia (hr)	7.3 ± 3.2 +‡	5.1 ± 2.2 *	12.5 ± 2.02	0.001
Number of morphine boluses	2 (1-2) +‡	2.5 (2-3) *	1 (0-1)	0.001
• Zero	0	0	8 (40)	
• 1	7 (35)	1 (5)	12 (60)	
• 2	11 (55)	9 (45)	0	
• 3	2 (10)	10 (50)	0	
PONV	5 (25) +‡	13 (65) *	2 (10)	0.001

*data presented as mean ± SD, median (quartiles), or numbers (%); PONV: Postoperative Nausea and Vomiting; * denotes significance between Vitamin C group and Combined group; + denotes significance between Melatonin group and Combined group; ‡ denotes significance between Melatonin group and Vitamin C group.*

[CI]) and standard deviation [SD] if normally distributed or median, and interquartile range if abnormally distributed.

Shapiro Wilk's test was used to evaluate the normal distribution of continuous data. Categorical measurements between groups were compared using the Chi-square test. Repeated measure analysis was used to assess the change over time of numerical measurements at different periods.

The Kolmogorov–Smirnov test was used to determine whether continuous variables had a specific distribution. Continuous data was analyzed using one-way analysis of variance (ANOVA) or Kruskal-Wallis test according to the normality of the data. Repeated measures were analyzed using ANOVA for repeated measures with post-hoc pairwise comparisons using Tukey's tests. The level of statistical significance (P value) in all tests was considered as 0.05.

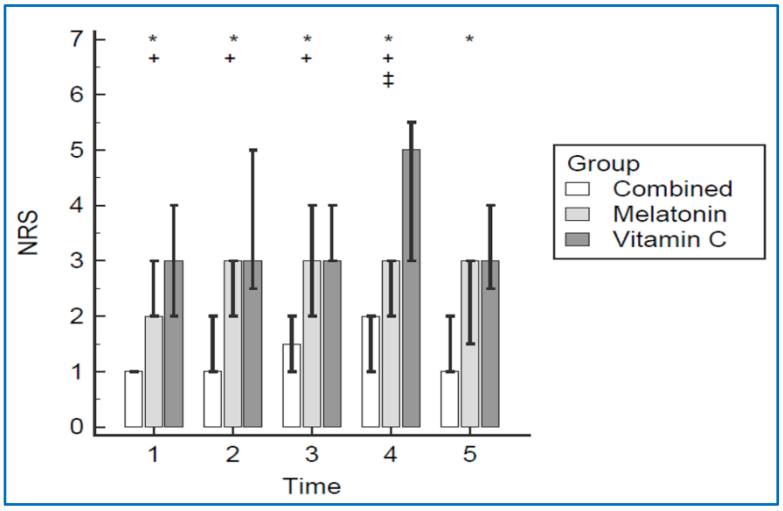

Figure 2: Numeric Rating Scale: Bars are medians, whiskers are 25th and 75th percentile; * denotes significance between Vitamin C and Combined groups; + denotes significance between Melatonin and Combined groups; ‡ denotes significance between Melatonin and Vitamin C groups; T1: 1 hour postoperative; T2: 2 hr; T3: 4 hr; T4: 12 hr; T5: 24 hr.

3. RESULTS

In this study, eighty-three patients undergoing elective major abdominal procedures with mid-line incisions under general anesthesia were enrolled. Twenty-three patients were excluded from the study, 15 of which didn't fulfill the inclusion criteria, while eight declined to participate. The remaining sixty patients were allocated to three groups, twenty patients each, who finalized the study (Figure 1).

No significant differences were found between groups regarding patients' demographic characteristics, recovery time, and surgery duration (Table 1). There were no significant differences between the groups regarding intraoperative or postoperative BP, HR, and arterial oxygen saturation.

The postoperative morphine consumption in the first 24 hours was significantly lower in Group CM than in Groups M and V, 16.7 mg ± 2.4, 20.98 mg ± 1.38,

Table 3: Comparative Richmond Agitation Sedation Scale (RASS) scores in the groups

Postop time (hr)	Melatonin group (n = 20)	Vit C group (n = 20)	Melatonin + Vit C group (n = 20)	P-value
1	-1 (-1, 0) ‡	0 (0, 1) *	-1 (-1, -2)	< 0.001
2	-1 (-1, 0) ‡	0 (0, 1) *	-1 (-2, -1)	< 0.001
4	0 (-1, 0) +	0 (0, 1) *	-1 (-1, 0)	0.029
12	0 (0, 0) ‡	1 (0, 1) *	0 (-1, 0)	< 0.001
24	0 (-1, 0) ‡	0 (0, 1) *	-1 (-1, 0)	< 0.001

*Data presented as median (quartiles); *denotes significance between Vitamin C group and Combined group; + denotes significance between Melatonin group and Combined group; ‡ denotes significance between Melatonin group and Vitamin C group*

and 24.36 mg ± 3.12 in Groups VM, M, and V, respectively (P < 0.001). There was also a significant difference between Groups M and V regarding morphine consumption at 24 hours (P < 0.001) (Table 2). Intraoperative fentanyl consumption was lower in Groups VM and M compared to Group C (P < 0.001 and = 0.012, respectively). However, there was no significant difference between Group CM and M (P = 0.193).

The time to first analgesic requirement during the first 24 h was significantly longer in the VM Group, 12 ± 2.02 (P < 0.001). It was also longer in Group M than in Group C, 7.3 ± 3.2 and 5.1 ± 2.2 respectively (P < 0.001).

The NRS pain score was lower in Group CM than in groups M and C at 1, 2, 4, and 12 hours postoperative (P < 0.001). At 24 hours postoperative, the NRS pain score was lower in Group CM than in Group C (P < 0.001), while the difference between Group CM and Group M at 24 hours was not statistically significant (P = 0.07). The difference between Groups V and M was comparable except at 12 hours postoperative, as the NRS was higher in Group C (Figure 2).

We found a significant difference between the three studied groups regarding PONV; the lowest incidence was in Group CM, and the highest one was in Group C (P < 0.001) (Table 2).

RASS score was lower in Group CM compared to Group C at 1, 2, 4, 12, and 24 hours postoperative (P < 0.001). It was also lower in Group M compared to Group C in all time points except at 12 hours postoperative (P = 0.106). RASS was lower in Group CM than in group M at 4 hours postoperative; however, it was comparable in both groups at 1, 2, 12, and 24 hours postoperative (Table 3).

None of the patients reported CPSP at one month or at three months postoperative.

4. DISCUSSION

In the present study, we found that 10 mg melatonin and 1 g vitamin C, given together two hours before surgery, reduced the postoperative morphine consumption, NSR scores, and the incidence of PONV compared to if either were given alone.

Administration of melatonin has a dose-dependent long-term anti-nociceptive effect in acute, neuropathic, and inflammatory pain. This is explained by exhibiting an effective change in pain threshold through attenuating nociceptive responses to various noxious stimuli. Several studies proved melatonin elevates β-endorphin levels within the central nervous system and interacts with the centrally located opioid, γ-aminobutyric acid (GABA), and N-methyl-D-aspartate receptor systems.[10] Moreover, melatonin reduces the elevated expression of nuclear factor kappa B (NF-kB) and inhibits the enhanced level of pro-inflammatory cytokines IL-6 or TNF-a to modulate neuroinflammation.[11]

Our results are consistent with previous reports on using melatonin as an adjuvant analgesic in abdominal surgeries. In which it was compared with placebo or various adjuvant analgesics. Kiabi FH et al. investigated the postoperative analgesic effect of melatonin in patients undergoing elective cesarean section under spinal anesthesia; they showed that melatonin 10 mg given one hour preoperatively decreased postoperative pain intensity, the time to require analgesia, and the opioid requirements with a shorter time to resume mobility.[12] Alkhfaji H et al. also reported the effect of melatonin on postoperative pain in patients who performed cesarean section; melatonin did not only decrease the postoperative pain severity and opioid requirements; it also reduced the intra- and postoperative blood loss.[13] Borazan H et al. reported that 6 mg of melatonin given the night before surgery and repeated 1 hour preoperatively decreased intraoperative fentanyl requirements, postoperative pain severity, and tramadol consumption, with better postoperative sleep quality and higher sedation scores.[14] Haryalchi et al. reported that 6 mg of melatonin orally given preoperatively had decreased the severity of postoperative pain.[15] On the other side, Khezri M et al. tested two doses of melatonin in patients undergoing cesarean section, and they found that melatonin did not improve analgesia. Nevertheless, it increased the incidence of postoperative headache with the higher dose.[16] Andersen LP et al. injected 10 mg of melatonin intravenously at the time of incision in patients undergoing laparoscopic cholecystectomy; they found no effect on pain intensity and analgesic usage.[17] This controversy may be referred to the type of surgery and

anesthesia or the different dosages or routes of administration.

Vitamin C could reduce postoperative pain through different mechanisms. They include its antioxidant characteristics, anti-inflammatory effect, neuroprotective effect, and involvement in collagen production.[18] It is also crucial for producing neurotransmitters like dopamine, epinephrine, and serotonin; they are essential for cholinergic and GABAergic neural transmissions. These neurotransmitters also play a role in inhibiting pain pathways.[19] It has proven to reduce the severity of acute pain and the prevalence of complex regional pain syndromes with its anti-nociceptive effect.[7]

Consistent with our results, Kumar A. et al. investigated the analgesic effect of vitamin C given orally at a dose of 2 gm administered the night before surgery and repeated 2 hours preoperatively in patients undergoing laparoscopic surgeries, they reported a reduction in postoperative pain intensity and opioid consumption.[20] Aboelelea M. et al. also reported the pain-reducing effect of vitamin C and the associated lower postoperative morphine consumption in patients who performed laparoscopic sleeve gastrectomy.[21] Jeon et al. injected 50 mg/kg of vitamin C immediately after anesthesia induction in patients undergoing laparoscopic colectomy; they found that vitamin C decreased the pain intensity in the first 24 hours postoperatively and reduced the total morphine consumption.[22] Moon et al. reported that adding magnesium to vitamin C was more effective in reducing postoperative pain than using each agent separately. ([23]) A meta-analysis searched the effect of vitamin C on postoperative analgesic consumption. It stated that perioperative use of vitamin C has shown a significant reduction in pain score and opioid requirement up to postoperative 24 hours.[19] Another meta-analysis has shown that the evidence on the postoperative pain-reducing effect of vitamin C and its role in reducing morphine consumption is of very low certainty, which cannot support a systematic use outside a research setting.[24]

Tunay et al. reported that preoperative administration of melatonin or vitamin C was associated with lower pain scores, analgesics consumption, and lower intensity of PONV compared to placebo in patients undergoing major abdominal surgeries; they suggest that the analgesic effect of the study drugs is referred to their interaction with morphine.[10]

Despite the several studies that have proven the pain-relieving effects of melatonin and vitamin C, it is still uncertain whether their combined analgesic effects are synergistic or additive in treating postoperative pain. To the extent of our knowledge, this is the first study that investigated the impact of combining both melatonin and vitamin C on postoperative pain, opioid consumption, and opioid adverse effects after major abdominal surgeries.

Managing postoperative pain is a significant concern, as studies show that up to 75% of patients report their pain levels as moderate, severe, or extreme. ([25])Effective control of acute pain is vital in preventing the development of CPSP.[26] Several studies have indicated a correlation between the severity of acute pain following surgery and the incidence of chronic pain.[27] However, balancing effective pain management with the need to minimize side effects from analgesics remains a challenge for physicians. Therefore, despite the efficacy of opioids, cases of insufficient pain management are not uncommon due to their adverse effects.[28] Current clinical guidelines advocate for a multimodal analgesia approach, which combines various analgesic medications and interventions. ([29]) In this context, combining melatonin and vitamin C could be a beneficial adjuvant to conventional analgesics.

5. LIMITATIONS

First, our study is a single-center study. Second, we did not measure the concentration of vitamin C or melatonin in serum pre- and post-medication administration. Finally, the lower prevalence of CPSP in abdominal surgeries warrants further studies, especially in surgeries with a higher incidence of CPSP, e.g., radical mastectomy.

6. CONCLUSION

In patients undergoing major abdominal surgery with mid-line incision, combined use of melatonin and vitamin C provides a synergistic analgesic effect in postoperative pain management with lower postoperative pain scores, opioid consumption, and the incidence of PONV, compared to using any of them alone.

7. Data availability

The numerical data related to this study is available with the authors.

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9. Conflict of interest

The authors report no conflict of interest.

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11. Authors' contribution

WH, KR, and MA were responsible for the idea's conception. WH, KR, Am K, and DS contributed to the study design. Ah K, Am K, and DS were responsible for data collection, analysis and interpretation, and manuscript writing. All authors read, revised, and approved the final manuscript. The corresponding author agreed to be accountable for all aspects of the work.

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