Section: General Surgery

Original Research Article

EFFECT OF INTRAOPERATIVE INFUSION OF ACETYLCYSTEINE ON ANALGESIC CONSUMPTION IN THE POSTOPERATIVE PERIOD

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ABSTRACT

Background: Postoperative pain continues to pose a significant issue despite progress in multimodal analgesia. Opioid analgesics are efficacious yet linked to undesirable effects, necessitating the exploration of safe opioid-sparing adjuncts. N-acetylcysteine (NAC), a precursor of glutathione with antioxidant and anti-inflammatory properties, has demonstrated potential analgesic effects by reducing oxidative stress and modulating glutamatergic neurotransmission. The aim & objective is to assess the efficacy of intraoperative intravenous N-acetylcysteine in diminishing postoperative analgesic needs and extending the duration until the initial rescue analgesia in patients undergoing general surgical interventions. **Materials and Methods:** A prospective comparison study was performed in the Department of General Surgery, Justice K. S. Hegde Charitable Hospital, NITTE (Deemed to be University), Mangalore, from May 2024 to October 2025. Sixty-two adult patients were divided into two groups (n=31 per group). Group A was administered intravenous N-acetylcysteine (150 mg/kg) throughout the operation, whereas Group B got standard perioperative treatment devoid of NAC. The principal outcomes were analgesic consumption postoperatively within 24 hours and the duration until the initial rescue analgesia was administered. Statistical analysis was conducted utilising SPSS version 20, with $p<0.05$ being statistically significant. **Result:** The baseline demographic variables were similar across the groups. The NAC group exhibited a markedly prolonged duration to initial rescue analgesia ($p<0.001$) and a substantially reduced postoperative analgesic usage (2.1±0.9 vs. 4.2±0.6 doses; $p<0.001$). Only 19% of patients in the NAC group needed four or more analgesic doses, in contrast to 77% in the control group ($\chi^2=19.87$, $p<0.001$). **Conclusion:** Intraoperative intravenous N-acetylcysteine markedly decreased postoperative analgesic needs and extended the duration of postoperative analgesia. NAC seems to be a safe and effective complement to multimodal analgesia in individuals undergoing general surgical operations. More extensive randomised controlled trials are necessary to validate these results.

INTRODUCTION

Postoperative pain continues to pose a significant issue in perioperative care, despite advancements in anaesthetic methods and multimodal analgesia. Approximately 70–80% of patients endure moderate-to-severe pain post-surgery, potentially hindering recovery, extending hospital duration, diminishing patient satisfaction, and elevating the risk of chronic postsurgical pain. Effective postoperative pain management is a crucial element of Enhanced Recovery After Surgery (ERAS) protocols, designed to promote early mobilisation while reducing opioid-related side effects.[1-3]

Multimodal analgesia integrates analgesics with diverse modes of action to enhance pain management while diminishing opioid usage. While opioids continue to be the foundation of postoperative pain management, their administration is linked to nausea, vomiting, drowsiness, respiratory depression, constipation, and the risk of dependence. As a result, extensive research has concentrated on discovering supplementary medicines that deliver efficient analgesia with reduced unwanted effects.[4]

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N-acetylcysteine (NAC) is a synthetic derivative of L-cysteine that restores intracellular glutathione levels and demonstrates significant antioxidant and anti-inflammatory effects. N-acetylcysteine (NAC) not only plays a recognised role in acetaminophen toxicity and the prevention of contrast-induced nephropathy, but it also modulates glutamatergic neurotransmission, inhibits oxidative stress, and suppresses pro-inflammatory cytokines associated with nociceptive pathways. These mechanisms indicate a possible use for NAC as a supplementary agent in perioperative pain control.[5,6]

Recent experimental and clinical investigations indicate that perioperative NAC administration may diminish surgical pain scores, reduce opioid use, and extend the duration of analgesia. Nonetheless, the existing information is constrained and contradictory owing to discrepancies in surgical techniques, dosage protocols, and research methodologies.[7–10] Consequently, additional clinical trials are necessary to determine its effectiveness in standard surgical practice.

This study aimed to assess the impact of intraoperative intravenous N-acetylcysteine on postoperative analgesic needs in individuals undergoing elective general surgery. We expected that intraoperative NAC delivery would decrease postoperative analgesic usage and extend the duration until the first rescue analgesia, in comparison to routine perioperative treatment.

MATERIALS AND METHODS

This prospective comparative study was carried out at the Department of General Surgery at Justice K. S. Hegde Charitable Hospital, NITTE (Deemed to be University), Mangalore, Karnataka, India, over 18 months from May 2024 to October 2025. The Institutional Ethics Committee approved the study before its initiation, and written informed consent was secured from all participants.

Study population: Sixty-two adult patients slated for elective general surgical operations under general anaesthesia were included. Patients were divided into two groups, each consisting of 31 individuals.

Group A (NAC group): Administered intravenous N-acetylcysteine (150 mg/kg) diluted in 250 mL of normal saline during the intraoperative period.

Group B (Control group): Received conventional perioperative care devoid of N-acetylcysteine.

Criteria for Inclusion

Patients were eligible for inclusion if they: Ranged in age from 18 to 65 years.

Scheduled for elective general surgical interventions under general anesthesia.

Classified as American Society of Anesthesiologists (ASA) physical status I or II.

Obtained written informed consent

Criteria for Exclusion: Patients were excluded if they possessed a documented allergy or hypersensitivity to N-acetylcysteine. Exhibited considerable hepatic, renal, cardiac, or respiratory impairment. Were undergoing chronic opioid therapy or long-term analgesic treatment. Experienced chronic pain disorders or psychological conditions that influenced pain evaluation.Were either pregnant or lactating.

Declined to engage in the study.

Anaesthetic Method

All patients received a standardised general anaesthesia protocol. Routine monitoring encompassed electrocardiography, non-invasive blood pressure measurement, pulse oximetry, and capnography. Anaesthesia was initiated and sustained in accordance with institutional standards. The intervention group received intravenous N-acetylcysteine (150 mg/kg) diluted in 250 mL of normal saline during surgery, while the control group underwent usual perioperative care without N-acetylcysteine. Postoperative analgesia was delivered in accordance with institutional standards, and rescue analgesics were given as clinically necessary.

Outcome measures

Primary Outcomes: Total analgesic usage postoperatively within the initial 24 hours.

Duration till the initial delivery of rescue analgesics post-surgery.

Secondary Outcomes: Quantity of rescue analgesic dosages administered within the initial 24 hours postoperatively.

Evaluation of postoperative analgesic needs across various surgical interventions.

Data Collection: Demographic characteristics such as age, sex, body mass index (BMI), and surgical type were documented. The duration to the initial rescue analgesia was recorded from the conclusion of surgery to the delivery of the first rescue analgesic. The cumulative quantity of postoperative analgesic dosages given within the initial 24 hours was documented.

Statistical Analysis: Data were input into Microsoft Excel and analysed utilising IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were represented as mean ± standard deviation (SD), whilst categorical variables were displayed as frequencies and percentages. The independent Student's t-test was employed to compare continuous variables between the two groups. Categorical variables were analysed with the Chi-square test or Fisher's exact test, as applicable. A p-value less than 0.05 was deemed statistically significant.

Ethical Considerations: The research adhered to the principles of the Declaration of Helsinki. Approval from the Institutional Ethics Committee was secured before patient recruitment, and written informed consent was acquired from all participants before enrollment.

RESULTS

The study had 62 patients, with 31 individuals assigned to Group A (N-acetylcysteine) and 31 to Group B (control). The baseline demographic features of the two groups were comparable, showing

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no statistically significant variations in age, body mass index (BMI), sex distribution, or medical history, hence confirming effective matching of study participants before the intervention.

Table 1: Baseline demographic and clinical characteristics of the study participants

Characteristic	Group A (n=31)	Group B (n=31)	p-value
Age (years), mean ± SD	48.7 ± 11.8	44.6 ± 12.1	0.183
BMI (kg/m²), mean ± SD	22.6 ± 4.4	23.9 ± 4.3	0.266
Height (cm), mean ± SD	162.3 ± 10.9	158.1 ± 8.6	—
Weight (kg), mean ± SD	60.6 ± 13.9	59.5 ± 11.3	—
Male, n (%)	22 (71.0)	22 (71.0)	1.000
Female, n (%)	9 (29.0)	9 (29.0)	—
Past medical history, n (%)	6 (19.4)	6 (19.4)	—

No statistically significant variations in baseline demographic or clinical variables were seen between the two groups ($p>0.05$), indicating that the study groups were adequately matched before the intervention.

Table 2: Comparison of postoperative analgesia-related outcomes

Outcome	χ^2	df	p-value	Interpretation
Time to first analgesia request	31.79	8	<0.001	Significant
Frequency of analgesic use	53.03	20	<0.001	Significant

Patients administered intraoperative N-acetylcysteine exhibited a markedly extended duration before the initial analgesic request and a considerably diminished incidence of postoperative analgesic use in comparison to the control group ($p<0.001$).

Table 3: Comparison of postoperative analgesic consumption during the first 24 hours

Parameter	Group A	Group B	p-value
Mean analgesic doses (24 h)	2.1 ± 0.9	4.2 ± 0.6	<0.001
Median analgesic doses	2	4	—
Total analgesic doses	~65	~130	—
Patients requiring ≥4 doses	6 (19%)	24 (77%)	<0.001

Patients in the NAC group necessitated markedly less postoperative analgesic dosages compared to the control group. The average analgesic requirement decreased by around 50%, and a considerably lower proportion of patients necessitated four or more rescue doses within the initial 24 hours (19% vs. 77%; $p<0.001$).

Table 4: Procedure-wise comparison of mean time to first analgesia request

Surgical procedure	Group A	Group B	p-value
EVLA	5 h	2 h	<0.05
Laparoscopic cholecystectomy	5 h	2 h	<0.001
Left inguinal hernia repair	5 h	2 h	<0.05
Right-sided hernia repair	6 h	45 min	<0.01
Split skin grafting	6 h	2 h	<0.05
Inguinal hernioplasty	3 h	1 h	0.10

The duration until the initial rescue analgesia was uniformly prolonged in the NAC group throughout the majority of surgical interventions. Statistically substantial enhancements were noted in patients after EVLA, laparoscopic cholecystectomy, left inguinal hernia repair, right-sided hernia repair, and split skin grafting. No substantial difference was noted for inguinal hernioplasty. Procedures with minimal sample sizes were omitted from comparative analysis.

Table 5: Summary of primary study outcomes

Outcome	Group A (NAC)	Group B (Control)	Statistical significance
Baseline characteristics	Comparable	Comparable	NS
Time to first rescue analgesia	Significantly prolonged	Earlier	p<0.001
Frequency of analgesic administration	Lower	Higher	p<0.001
Mean analgesic consumption	Lower	Higher	p<0.001
Patients requiring ≥4 analgesic doses	19%	77%	p<0.001

Intraoperative intravenous N-acetylcysteine markedly decreased postoperative analgesic needs and extended the duration of postoperative analgesia. Patients administered NAC necessitated fewer rescue analgesics and encountered a postponed onset of surgical pain relative to those getting conventional perioperative treatment.

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DISCUSSION

This study indicated that intraoperative intravenous N-acetylcysteine (NAC) markedly diminished postoperative analgesic needs and extended the duration until the first rescue analgesia in patients undergoing elective general surgery. The baseline demographic variables, such as age, BMI, sex, and medical history, were similar across the two groups, suggesting that the differences in postoperative analgesic results were due to the intervention rather than initial factors.

Patients in the NAC group necessitated markedly fewer postoperative analgesic doses during the initial 24 hours compared to the control group (2.1 ± 0.9 vs. 4.2 ± 0.6 doses, $p<0.001$). Likewise, only 19% of patients in the NAC group necessitated four or more doses of rescue analgesics, in contrast to 77% in the control group. The findings align with the randomised controlled experiment conducted by Mulkens et al., which indicated that perioperative NAC treatment markedly diminished postoperative pain scores and opioid usage by mitigating oxidative stress and central sensitisation.[11]

The duration until the initial rescue analgesia was markedly extended in the NAC group, especially in patients having laparoscopic cholecystectomy, EVLA, hernia repair, and split skin grafting. Wilson et al. found similar outcomes, noting delayed postoperative analgesic needs and reduced opioid intake after intraoperative NAC delivery. Similarly, El Hamamsy et al. reported that intravenous NAC enhanced postoperative analgesia and diminished opioid needs following abdominal surgery.[12,13]

The advantageous analgesic effect of NAC is probably associated with its antioxidant and anti-inflammatory characteristics. NAC restores intracellular glutathione levels, diminishes reactive oxygen species, reduces the activation of nuclear factor-kappa B (NF-κB), and modifies glutamatergic neurotransmission, consequently alleviating peripheral and central sensitisation linked to surgical tissue injury.[14,15] These mechanisms offer a biological rationale for the diminished analgesic intake noted in the current investigation.

This study has specific limitations. The study was performed at a single centre with a limited sample size, and pain severity was evaluated indirectly via analgesic requirements instead of through sequential validated pain levels. The variability of surgical procedures may have affected postoperative analgesic requirements. Extensive multicenter randomised controlled studies employing standardised surgical techniques and verified pain rating instruments are necessary to validate these findings.

The data indicate that intraoperative intravenous NAC is a safe and effective complement to multimodal analgesia and may aid in opioid-sparing postoperative pain management for patients having elective general surgical operations.

CONCLUSION

This study revealed that intraoperative intravenous N-acetylcysteine (NAC) markedly diminished postoperative analgesic needs and extended the duration until the first rescue analgesia in patients undergoing elective general surgery. Patients with NAC necessitated fewer rescue analgesic doses within the initial 24 hours compared to the control group, signifying enhanced postoperative pain management. These data endorse the efficacy of NAC as a valuable complement to multimodal analgesia, presumably via its antioxidant and anti-inflammatory properties that mitigate central sensitization and postoperative pain perception. Due to its advantageous safety profile and ability to reduce opiate use, intraoperative NAC may be regarded as a valuable enhancement to perioperative pain management approaches. Nonetheless, extensive multicenter randomized controlled studies employing standardized surgical techniques and prolonged follow-up are necessary to validate these results and determine the best dose regimen prior to widespread clinical application.

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