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Article Original

Benefits of Ketamine-Lidocaine Combination for Postoperative Analgesia.

Bénéfices de l'association kétamine-lidocaïne pour l'analgésie postopératoire.

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Résumé

Contexte : La gestion de la douleur postopératoire demeure un défi majeur en chirurgie digestive oncologique. L'utilisation modernisée de la kétamine et de la lidocaïne avec différents dosages et techniques d'administration a amélioré la prise en charge de la douleur chez les patients chirurgicaux.

Méthodes : Cette étude prospective randomisée a inclus 130 patients répartis en deux groupes : groupe lidocaïne (n=65) et groupe lidocaïne-kétamine (n=65). Les patients étaient programmés pour une chirurgie digestive oncologique par laparotomie. Le critère de jugement principal était la consommation totale de morphine systémique le premier jour postopératoire.

Résultats : La consommation totale de morphine systémique le premier jour postopératoire était significativement plus faible dans le groupe lidocaïne-kétamine ($5 \text{ mg} \pm 2$ vs $15 \text{ mg} \pm 5$; $p < 0,001$). La consommation globale de morphine jusqu'au troisième jour postopératoire était également réduite ($10 \text{ mg} \pm 9$ vs $30 \text{ mg} \pm 10$; $p < 0,001$). Le groupe lidocaïne-kétamine a présenté moins d'effets secondaires liés aux opioïdes (12 % vs 27 % ; $p < 0,001$) et des scores de douleur significativement plus faibles.

Conclusion : L'association lidocaïne-kétamine est plus efficace que la lidocaïne seule pour réduire la consommation d'opioïdes en période postopératoire chez les patients subissant une chirurgie digestive oncologique majeure par laparotomie.

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Mots clés : analgésie postopératoire ; lidocaïne ; kétamine ; récepteurs NMDA ; épargne opioïde.

Abstract

Background: Postoperative pain management remains a major challenge in oncological digestive surgery. The modernized use of ketamine and lidocaine with different dosages and administration techniques has improved pain management in surgical patients.

Methods: This prospective randomized study included 130 patients divided into two groups: lidocaine group (n=65) and lidocaine-ketamine group (n=65). Patients were scheduled for oncological digestive surgery via laparotomy. The primary endpoint was total systemic morphine consumption on the first postoperative day.

Results: Total systemic morphine consumption on the first postoperative day was significantly lower in the lidocaine-ketamine group ($5 \text{ mg} \pm 2$ vs $15 \text{ mg} \pm 5$; $p < 0.001$). Overall morphine consumption until the third postoperative day was also reduced ($10 \text{ mg} \pm 9$ vs $30 \text{ mg} \pm 10$; $p < 0.001$). The lidocaine-ketamine group experienced fewer opioid-related side effects (12% vs 27%; $p < 0.001$) and significantly lower pain scores.

Conclusion: The lidocaine-ketamine combination is more effective than lidocaine alone in reducing opioid consumption in the postoperative period in patients undergoing major oncological digestive surgery via laparotomy.

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keywords: postoperative analgesia; lidocaine; ketamine; NMDA receptors; opioid-sparing.

Introduction

Postoperative pain represents a major challenge in oncological digestive surgery patient management. Despite therapeutic advances, it remains inadequately controlled in numerous cases, leading to postoperative complications and increased morbidity¹.

Multimodal analgesia currently represents the gold standard in postoperative pain management². This approach combines different therapeutic classes acting on distinct nociceptive mechanisms, optimizing analgesic efficacy while minimizing side effects³.

Lidocaine, a local anesthetic of the amide family, possesses demonstrated analgesic properties when administered intravenously⁴. Its mechanism of action involves blocking voltage-gated sodium channels, thereby reducing nociceptive transmission⁵. Clinical studies have demonstrated that perioperative intravenous lidocaine administration allows for significant reduction in opioid consumption and postoperative pain intensity⁶.

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, exhibits analgesic properties at sub-anesthetic doses⁷. Its use in the perioperative period has shown benefits in terms of postoperative pain reduction and hyperalgesia prevention⁸. NMDA receptors play a central role in central sensitization and hyperalgesia phenomena, explaining the interest in their antagonism for preventing chronic postoperative pain⁹.

The lidocaine-ketamine combination presents theoretical interest through the potential synergy of their complementary mechanisms of action¹⁰. Literature data suggest that this association could optimize analgesic efficacy while reducing the side

effects of each molecule used individually¹¹.

Objectives: The primary objective of this study was to demonstrate the superiority of the lidocaine-ketamine combination over lidocaine alone in multimodal analgesia for oncological digestive surgery. The secondary objective was to evaluate the impact on postoperative nausea and vomiting (PONV) occurrence.

MATERIALS AND METHODS

Study Design

Prospective, randomized, double-blind, single-center study.

Study Period

The study was conducted over a 12-month period within the oncological digestive surgery department.

Study Population

Inclusion Criteria

- Patients aged over 18 years
- Scheduled oncological digestive surgery via laparotomy
- Informed consent obtained

Exclusion Criteria

- Contraindications to analgesics used in the protocol
- Emergency surgery
- Refusal to participate
- Cognitive disorders preventing pain assessment

Sample Size Calculation

Sample size calculation was performed considering a clinically significant difference of 30% in morphine consumption, with 80% power and 5% alpha risk. The required number of subjects was 60 patients per group, increased to 65 to account for dropouts.

Randomization and Protocol

The 130 patients were randomly allocated into two groups:

- Lidocaine group (n=65): Lidocaine 1.5 mg/kg at induction then 1 mg/kg/h until extubation
 - Lidocaine-ketamine group (n=65): Lidocaine 1 mg/kg at induction then 0.5 mg/kg/h until extubation + Ketamine 0.25 mg/kg at induction then 0.125 mg/kg/h until extubation
- Multimodal analgesia also included: paracetamol 1g infusion 30 minutes before surgical closure then 1g/6h for 8h, nefopam 20 mg/12h, and titrated morphine according to pain scale.
- PONV prevention protocol followed the Apfel score: dexamethasone 8mg at induction if Apfel score < 2.

Outcome Measures

Primary Outcome

Total systemic morphine consumption during the perioperative period and on the first postoperative day.

Secondary Outcomes

- Morphine consumption until the third postoperative day
- Percentage of opioid-related side effects
- Pain scores (NRS, VAS) in the Post-Anesthesia Care Unit (PACU) and on the first, second, and third postoperative days
- PONV incidence

Statistical Analysis

Statistical analysis was performed using R software. Quantitative variables were expressed as means ± standard deviations and compared using Student's t-test. Qualitative variables were compared using the chi-square test. The significance threshold was set at $p < 0.05$.

RESULTS

Demographic and Clinical Characteristics

The mean age of patients was 58.35 ± 12.4 years in the lidocaine-ketamine group and 64.73 ± 10.8 years in the lidocaine group. Gender distribution was balanced with a sex ratio of 0.93 in the lidocaine-ketamine

group and 0.76 in the lidocaine group. Mean body mass index was comparable between both groups (22.59 ± 3.2 vs 23.09 ± 4.1 kg/m²).

Table 1: Demographic and Clinical Characteristics of Patients (n=130, Algiers University Hospital, 2024)

Characteristics	Lidocaine-Ketamine (n=65)	Lidocaine (n=60)	P
Age (years)	58.35 ± 12.4	64.73 ± 10.8	0.08
Gender F/M (n)	31/29	34/26	0.52
BMI (kg/m²)	22.59 ± 3.2	23.09 ± 4.1	0.43
ASAscore (median)	2	2	0.67
LEEscore (median)	1	1	0.82
Apfelscore (median)	1	2	0.15

Both groups were comparable in terms of age, gender, body mass index, cardiovascular risk (LEE score), anesthetic risk (ASA score), and predictive risk of PONV occurrence (Apfel score).

Surgical Characteristics

Table 2: Surgical Characteristics by Group (n=130, Algiers University Hospital, 2024)

Type of Surgery	Lidocaine - Ketamine (%)	Lidocaine (%)
Right Colectomy (RC)	33.33	30.66
Colorectal Resection (CRR)	16.66	13.33
Gastrectomy (G)	15.00	11.66

Hepatectomy (H)	20.00	31.33
Pancreatectomy (P)	15.00	13.33

Mean operative duration was 163 ± 45 minutes in the lidocaine-ketamine group and 128.2 ± 52 minutes in the lidocaine group ($p = 0.875$). This difference was not statistically significant.

Morphine Consumption

Total systemic morphine consumption on the first postoperative day was significantly lower in the lidocaine-ketamine group compared to the lidocaine group ($5 \text{ mg} \pm 2$ vs $15 \text{ mg} \pm 5$; $p < 0.001$). This difference represented a 67% reduction in morphine consumption.

Overall morphine consumption until the third postoperative day was also significantly reduced in the lidocaine-ketamine group ($10 \text{ mg} \pm 9$ vs $30 \text{ mg} \pm 10$; $p < 0.001$), representing a 67% reduction.

Side Effects and Pain Scores

The lidocaine-ketamine group had significantly fewer opioid-related side effects compared to the lidocaine group (12% vs 27%; $p < 0.001$). These side effects mainly included nausea, vomiting, constipation, and somnolence.

Pain scores were significantly lower in the lidocaine-ketamine group on the day of surgery and during the PACU stay (2 ± 3 vs 5 ± 3 ; $p < 0.001$).

Postoperative Nausea and Vomiting

The incidence of PONV was higher in the lidocaine-ketamine group (88.33% vs 15%; $p = 0.002$). This difference was statistically significant and represented a notable side effect of the combination.

DISCUSSION

Discussion of Study Results

Our study demonstrates the superiority of the lidocaine-ketamine combination over lidocaine alone in reducing postoperative morphine consumption. The 67% reduction in morphine consumption on the first postoperative day is clinically significant and is accompanied by improved pain scores¹².

This efficacy can be explained by the synergy of the two molecules' mechanisms of action. Lidocaine, through its action on sodium channels, reduces peripheral and central nociceptive transmission¹³. Ketamine, by antagonizing NMDA receptors, prevents central sensitization and hyperalgesia phenomena¹⁴. This dual action allows for more complete and durable analgesia.

The significant reduction in opioid-related side effects (from 27% to 12%) constitutes a major clinical benefit.

This reduction is explained by the morphine-sparing effect of the combination, allowing for reduced opioid doses required¹⁵.

Study Strengths

This study presents several methodological strengths. The randomized controlled design allows for establishing a causal relationship between the intervention and observed results. The sample size calculated according to statistical rules provides adequate power to the study.

The homogeneous population of oncological digestive surgery patients limits confounding bias.

The multimodal evaluation including morphine consumption, pain scores, and side effects offers a comprehensive view of therapeutic efficacy.

Follow-up until the third postoperative day allows for evaluating the short-term impact of the intervention.

Study Limitations

Several limitations must be highlighted. The significant increase in PONV incidence in the lidocaine-ketamine group (88.33% vs 15%) constitutes a major side effect that may limit the acceptability of this combination. This high incidence could be related to the emetogenic properties of ketamine, even at sub-anesthetic doses¹⁶.

The single-center study limits the generalizability of results. The absence of complete blinding for investigators could introduce evaluation bias, although objective criteria (morphine consumption) are less sensitive to this bias.

The limited follow-up duration of three days does not allow for evaluating the impact on chronic postoperative pain and long-term functional rehabilitation.

Comparison with Literature

Our results are consistent with recent literature data. The study by Weibel et al. (2021) reported a 45% reduction in morphine consumption with the lidocaine-ketamine combination compared to lidocaine alone¹⁷. Our 67% reduction is superior, possibly due to the dosages used and the studied population.

Zhang et al. (2023) demonstrated similar results with significant reduction in pain scores and opioid consumption¹⁸. Their study, however, reported a lower PONV incidence (35% vs 88.33% in our study), suggesting interindividual variability or protocol differences.

Recent meta-analyses confirm the efficacy of this combination¹⁹. Brinck et al. (2021) reported an average 40% reduction in morphine consumption with the lidocaine-ketamine combination, corroborating our results²⁰.

The high PONV incidence observed in our study differs from literature data. This difference could be explained by the

ketamine dosages used, the studied population, or PONV prevention protocols. Dosage adjustments or optimization of antiemetic prophylaxis could reduce this side effect.

CONCLUSION

This study demonstrates that the lidocaine-ketamine combination is more effective than lidocaine alone in reducing opioid consumption in the postoperative period in patients undergoing major oncological digestive surgery via laparotomy. The 67% reduction in morphine consumption is accompanied by improved pain scores and decreased opioid-related side effects.

However, the high PONV incidence constitutes an important limitation that requires optimization of antiemetic protocols. This combination represents a promising approach to multimodal analgesia, subject to better control of side effects.

Multicenter studies with larger sample sizes and long-term follow-up are necessary to confirm these results and evaluate the impact on functional rehabilitation and chronic postoperative pain.

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