



RESEARCH ARTICLE

REVISED Ketamine infiltration improves analgesia after thyroid surgery [version 2; peer review: 1 approved, 2 approved with reservations]

Previously titled: Ketamine infiltration decreases the need for opioids after thyroid surgery

Moncef Sellami ¹⁻³, Imen Zouche ^{1,2,4}, Mariam Ben Ayed ¹⁻³,
Maroua Bouhali^{1,2,4}, Khadija Ben Ayed^{1,2,4}, Salma Ktata^{1,2,4},
Boutheina Hammami¹⁻³, Mohamed Amine Chaabouni ¹⁻³, Ilhem Charfeddine¹⁻³

¹Faculty of Medicine of Sfax, Sfax, Tunisia

²University of Sfax, Sfax, Tunisia

³Department of Otorhinolaryngology, Head and Neck Surgery, Habib Bourguiba University Hospital, Sfax, Tunisia

⁴Department of Anesthesia, Habib Bourguiba University Hospital, Sfax, Tunisia

V2 First published: 23 Feb 2023, 12:206
<https://doi.org/10.12688/f1000research.127562.1>

Latest published: 18 Aug 2023, 12:206
<https://doi.org/10.12688/f1000research.127562.2>

Abstract

Background: Postoperative pain increases the risk of postoperative complications and may predispose patients to chronic post-surgical pain. This study aims to evaluate the impact of ketamine wound infiltration versus placebo at the end of thyroid surgery on postoperative pain and analgesic requirements.

Methods: In this randomized controlled trial, we prospectively studied patients who underwent thyroid surgery. Patients were randomized into two groups: group S, where local infiltration was performed using 10 ml of a physiological saline solution; and group K, where 10 ml of a solution containing 2 mg/kg ketamine was infiltrated. Standardized thyroidectomies were performed in the 2 groups. Pain perception was measured using a visual analog scale (VAS) every 10 minutes in the post-anesthetic care unit (PACU) for 2 hours and thereafter every 6 hours during the first 24 hours. The opioid requirement in the PACU was evaluated. A comparison between the 2 groups was carried out.

Results: Postoperatively, the mean VAS was higher in group S compared to group K during all PACU stay periods and the first 24 hours. Pain scores during swallowing were significantly lower for group K in the PACU at 0, 10, and 20 minutes. The mean morphine consumption in the PACU was 0.71 mg and 0 mg respectively in group S and group K ($p=0.03$). The incidence of nausea and vomiting was similar in both groups.

Conclusions: Ketamine wound infiltration is an efficient modality to reduce postoperative opioid consumption compared to a placebo after thyroid surgery.

Open Peer Review

Approval Status

	1	2	3
version 2 (revision) 18 Aug 2023	 view		 view
version 1 23 Feb 2023	 view	 view	

- Chihebeddine Romdhani** , Military Hospital of Tunis, Tunis, Tunisia
Universite de Tunis El Manar, Tunis, Tunisia
Widd Kaabi, Universite de Tunis El Manar, Tunis, Tunisia
- Mohamed Kahloul**, University of Sousse, Sousse, Tunisia
- Pham Quang Minh**, Hanoi Medical University, Hanoi, Vietnam

Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Ketamine, thyroid surgery, wound infiltration, analgesia

Corresponding author: Moncef Sellami (sellami_moncef@yahoo.fr)

Author roles: **Sellami M:** Data Curation, Formal Analysis, Methodology, Resources, Supervision, Validation, Writing – Original Draft Preparation; **Zouche I:** Data Curation, Formal Analysis, Methodology, Validation, Writing – Original Draft Preparation; **Ben Ayed M:** Methodology, Writing – Original Draft Preparation; **Bouhali M:** Investigation, Methodology, Supervision, Validation, Visualization, Writing – Original Draft Preparation; **Ben Ayed K:** Conceptualization, Methodology; **Ktata S:** Validation, Writing – Original Draft Preparation; **Hammami B:** Supervision, Validation, Writing – Original Draft Preparation; **Chaabouni MA:** Conceptualization, Methodology, Writing – Original Draft Preparation; **Charfeddine I:** Validation, Writing – Original Draft Preparation

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2023 Sellami M *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Sellami M, Zouche I, Ben Ayed M *et al.* **Ketamine infiltration improves analgesia after thyroid surgery [version 2; peer review: 1 approved, 2 approved with reservations]** F1000Research 2023, 12:206 <https://doi.org/10.12688/f1000research.127562.2>

First published: 23 Feb 2023, 12:206 <https://doi.org/10.12688/f1000research.127562.1>

REVISED Amendments from Version 1

This revised article features notable improvements. The title has been refined to “Ketamine infiltration improves analgesia after thyroid surgery,” accurately encapsulating the essence of the study.

Methodologically, difficult airways were considered as an exclusion criterion, and we specified the ketamine concentration used, which was 50 mg/ml.

We defined that rescue analgesic during hospitalization was Nefopam in the case of VAS values greater than 30.

The randomization method was specified.

Our data, including age and type of surgery, have been carefully validated.

We improved the discussion according to the recommendations of the reviewers.

Any further responses from the reviewers can be found at the end of the article

Introduction

Thyroid surgery is known to be responsible for mild to moderate postoperative pain during the first 24 hours after surgery.¹ Postoperative pain can result in significant discomfort, delay in hospital discharge, and the development of chronic pain.² Postoperative pain control is fundamental for better recovery and quick return to daily activities. Opioids are effective for postoperative analgesia, but they cause sedation, respiratory depression, nausea, and vomiting.³ The modern concept in pain management includes a multimodal approach that involves the use of systemic analgesics associated with locoregional anesthesia techniques to reduce postoperative pain and opioid requirement.^{4,5} The locoregional anesthesia technique has mainly included bilateral superficial cervical plexus block and local wound infiltration with a local anesthetic agent.^{1,6,7} Bilateral block of the superficial cervical plexus is an effective technique that ensures better postoperative analgesia and has been widely used in thyroid surgery.^{6,8} Wound infiltration with a local anesthetic agent is a simple and safe procedure for reducing post-operative pain.^{6,7} In the current literature, different anesthetic agents for thyroid surgery wound infiltration were studied, including bupivacaine, diclofenac, ropivacaine, and, more rarely, ketamine.^{9–12}

Ketamine has a high affinity for N-methyl-D-aspartate receptors; it can also bind to opioid mu and sigma receptors that provide central and peripheral analgesic effects.¹³

The purpose of this study was to assess the impact of local wound infiltration using ketamine at the end of thyroid surgery on postoperative pain and opioid requirement.

Methods**Selection of patients, ethical approval and consent**

Ethical approval for this study was given by the Committee for the Protection of People in Southern Tunisia (approval number 0117/18). This randomized double-blind study was achieved through collaboration between the ENT department and the anesthesia department of the university hospital, Habib Bourguiba in Sfax, Tunisia.

Patients scheduled for thyroid surgery were enrolled after having provided written informed consent, which they also gave for publication of their data, in de-identified form.

Patients aged 18 to 65 years were included in this study if they had an ASA score (American Society of Anesthesiology) of I or II. Patients with unstable diabetes, an allergy to study drugs, a history of previous cervical surgery, or a history of cardiac or respiratory disease, as well as patients on long-term analgesics or corticosteroids and patients with predictable difficult airways were not included in this study. Patients who had major complications, such as allergic reactions to anesthetic drugs and major bleeding, as well as patients whose intubation required more than 2 attempts or whose surgery duration exceeded 3 hours, were excluded from this study. Patients who underwent a neck dissection associated with thyroid surgery were also excluded from the study.

The patients and randomization

The patients were informed about the anesthetic protocols and were educated about the use of the visual analog scale (VAS) to evaluate the severity of the pain. All patients in the study were blinded to the drug they received for postoperative pain.

The patients were randomly assigned to the following two groups using an online random list generator (<https://www.random.org>): group K represents wound infiltration using 10 ml of a solution containing 2 mg/kg of ketamine (KETAMINE PANPHARMA® 50 mg/ml) and group S (placebo group) represents wound infiltration using 10 ml of normal saline solution. The wound injection was performed at the end of the surgery after the skin suture.

General anesthesia procedure

After 3 minutes of preoxygenation, anesthesia was induced with an injection of 3 µg/kg of Fentanyl followed by 3 mg/kg of Propofol; and with intubation using a silicone wire-reinforced tracheal tube with 0.2 mg/kg Cisatracurium. Anesthesia was maintained using isoflurane with a minimum alveolar concentration (MAC) of 1% in a 50% oxygen/air mixture. A 0.03 mg/kg Cisatracurium bolus was administered every 40 min, and a Fentanyl bolus of 0.1 µg/kg was injected whenever there was an increase of 20% of the base values in heart rate or systolic arterial blood pressure.

Before surgery, an anesthesiologist, not involved in the study, prepared an unlabeled sterile syringe using 10 ml of ketamine (2 mg/kg) or 10 ml of a saline solution. After wound closure, the infiltration was performed by a blinded surgeon. The needle was introduced to a depth of 0.5 cm, an aspiration was then performed to avoid an intravascular injection followed by infiltrating the wound. The content of the syringe was used for homogenous infiltration of the subcutaneous wound sides by the surgeon.

Analgesic protocol

Thirty minutes before the end of the surgery, all patients received 1 g of paracetamol and then were extubated before being moved to the post-anesthetic care unit (PACU) for close monitoring for 2 hours. In the PACU, intravenous morphine titration (2 mg every 5 min) was performed until the VAS value was less than 30. All patients were admitted for at least 24 hours postoperatively in the ENT department. They all received 1 g of paracetamol systematically every 6 hours during the first 24 hours. Nefopam (NEFOMED 20 mg in 30 minutes) was administered when VAS was greater than 30. An anesthesiologist blinded to the study groups collected intraoperative and postoperative parameters.

Evaluation criteria

The primary outcomes were to determine the intensity of the pain using VAS from 0-100 in the first 24 hours. The VAS score was assessed every 10 minutes in the PACU for 2 hours and every 6 hours during the first 24 hours after the operation in the ENT department. Nefopam was administered in the cases where VAS exceeded 30. Opioid requirements were recorded during the PACU admission period. The occurrence of side effects of opioids and ketamine was noted.

Statistical analysis

In each group, a total number of 27 patients was required to obtain a difference on the VAS scale of 20 mm (standard deviation of 25 mm), with a power of 0.9 and an $\alpha=0.05$. To allow for some margin of error in the underlying assumptions, the baseline sample size was increased by 10 % to 32 patients per group. χ^2 test or Fisher statistical tests were used for the analysis of qualitative variables and the Student's T test for the analysis of quantitative variables (sample size of more than 30 patients per group; normality was typically ensured by the central limit theorem). A p-value < 0.05 was considered statistically significant (one-tailed test). Data entry and statistical analysis of data were performed with the software version 20 of Statistical Package for Social Sciences (SPSS) for Windows (SPSS Inc., Chicago, IL, USA).

Results

Study population

The study lasted for a total of 6 months from September 2018 to March 2019. Sixty-four patients were included. Two patients were withdrawn from the study for prolonged surgery (more than 3 hours). The flow of patients is represented in the CONSORT diagram of the study, which is shown in [Figure 1](#). Demographic and intraoperative characteristics of patients are represented in [Table 1](#).

Assessment of postoperative pain

Pain scores during swallowing were significantly lower for group K in the PACU at 0, 10, and 20 minutes ([Table 2](#)).

Regarding the first 24-hour postoperative hospitalization period in the ENT department, the mean VAS values were higher in group S compared to group K; either at rest or during swallowing, but the difference was not statistically significant ($p>0.05$) ([Table 3](#)).

None of the patients in group K received morphine while it was administered to four patients in group S. The mean morphine consumption in the PACU was 0.71 mg and 0 mg respectively in group S and group K. The difference in morphine consumption between both groups was statistically significant ($p=0.04$). Nefopam was not administered to any of our patients.

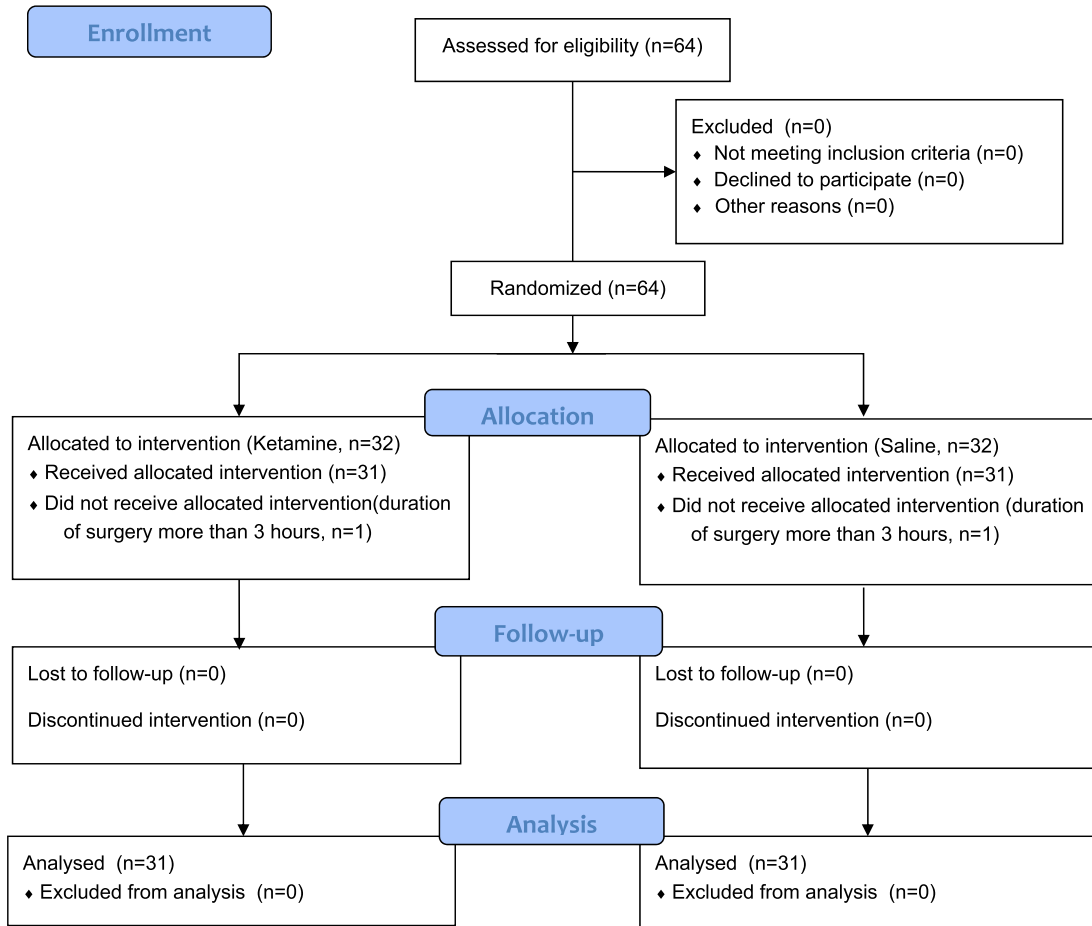


Figure 1. CONSORT 2010 flow chart for the patients in the study.

Table 1. Demographic characteristics and intraoperative anesthetic characteristics of both groups.

		Group S (N=31)	Group K (N=31)	P value
Demographic characteristics	Age (years)	47.9±13	41.8±38.5	0.04*
	Sex (M/F ratio)	3/28	1/30	0.3†
	Size (cm)	166±3	167±4	0.3*
	Weight (kg)	64.7±3.6	65±8	0.4*
The performed thyroid surgery	Total/partial thyroidectomy	14/17	24/7	0.009‡
Intraoperative anesthetic parameters (at 60 minutes)	HR (bpm)	72.9±8	72.7±11	0.3*
	SBP (mmHg)	94.7±15	98±14.6	0.4*
	MAP (mmHg)	70.7±10.4	75.2±10	0.15*
	DBP (mmHg)	58.6±9.5	63.2±10.2	0.1*
	SpO ₂ (%)	99.6±0.8	99.7±0.6	0.1*
	PetCO ₂ (%)	34.6±1.8	34.6±2.9	0.4*
Surgery duration	(minutes)	112±2	107±13	0.09*

Values are mean±standard deviation.

S: physiological serum, K: ketamine, cm: centimeters, kg: kilograms, HR: heartbeat, bpm: beats per minute, SBP: systolic blood pressure, MAP: mean arterial pressure, DBP: diastolic blood pressure, SpO₂: oxygen saturation, PetCO₂: Post apneic end-tidal carbon dioxide pressure.

*Student t-test.

†Fisher exact test.

‡χ² test.

Table 2. Mean VAS values in group S and group K at rest and during swallowing in the PACU admission period.

Timing (minutes)	VAS values at rest in the first 2 hours postoperatively			VAS values during swallowing in the first 2 hours postoperatively		
	Group S	Group K	P value	Group S	Group K	P value
0	4.52	1.94	0.05	6.13	2.58	0.04
10	3.87	1.94	0.08	6.45	2.58	0.04
20	3.87	1.94	0.08	6.77	2.58	0.03
30	4.52	2.58	0.12	7.10	3.23	0.05
40	4.84	2.58	0.16	6.13	2.90	0.05
50	4.19	2.58	0.19	6.13	3.23	0.08
60	3.87	2.58	0.19	5.81	3.23	0.09
70	3.87	2.58	0.15	5.81	3.23	0.09
80	4.19	3.23	0.27	6.77	3.87	0.09
90	3.87	3.23	0.33	6.13	3.87	0.1
100	3.87	3.23	0.3	6.13	3.55	0.09
110	4.19	3.23	0.26	6.45	3.55	0.07
120	4.19	3.23	0.26	6.45	3.55	0.07

Group S: saline solution group, group K: ketamine group, VAS: visual analog scale, PACU: post anesthetic care unit.

Table 3. Mean VAS values in group S and group K at rest and during swallowing in the first 24 hours postoperatively.

Timing (hours)	VAS values at rest in the first 24 hours postoperatively			VAS values during swallowing in the first 24 hours postoperatively		
	Group S	Group K	P value	Group S	Group K	P value
6	3.87	2.9	0.2	4.52	4.52	0.5
12	3.55	2.9	0.3	4.19	4.19	0.5
18	3.55	2.58	0.2	4.84	4.19	0.3
24	3.55	2.58	0.2	4.84	3.55	0.2

Group S: saline solution group, Group K: ketamine group, VAS: visual analog scale.

No patient presented a hematoma at the injection points of the product. A patient in group K showed hallucinations during the stay in the PACU. Dizziness was recorded in three patients of group K and one patient of group S. No patients presented postoperative shivers.

Respiratory distress was not recorded in any of our patients. Nausea and vomiting were observed in a total of 11 patients but without significant differences between both groups.

Discussion

Acute pain is one of the most common complaints after surgery. Thyroid surgery is known to be responsible for mild to moderate postoperative pain during the first 24 hours, with a mean VAS score of 6.9 (± 1.7).^{1,14} Pain following thyroid surgery has several origins: surgery-induced inflammatory lesions, intraoperative neck hyperextension, postoperative drainage, incision site, and laryngotracheal mobilization at swallowing.^{15,16}

The attempted locoregional anesthetic approaches to reduce post-thyroidectomy pain have included mainly bilateral superficial cervical plexus block and local wound infiltration with a local anesthetic agent.^{1,6,7}

Wound infiltration with a local anesthetic agent is a simple and safe procedure to reduce postoperative pain with fewer side effects in comparison with cervical plexus block.^{6,7} Several molecules were used to infiltrate the thyroidectomy wound. Bupivacaine has been reported to effectively reduce post-thyroidectomy pain.^{10,16,17} Sellami *et al.*¹⁰ concluded

that infiltration of bupivacaine wounds is effective in reducing pain perception and opioid requirements after thyroidectomy. In a recent meta-analysis, Jiang *et al.*¹⁷ recommended performing a local infiltration using bupivacaine before or after skin closure, 20 to 75 mg, as it significantly reduced postoperative pain and decreased rescue analgesic requirements.

Diclofenac has also been reported as an effective molecule to infiltrate the wound prior to surgery compared to Bupivacaine in reducing postoperative pain.¹¹ In a randomized controlled trial, numerical rating scale pain scores were significantly lower during the initial 24 hours after radical thyroidectomy in the group that received pre-incision ropivacaine infiltration and postoperative flurbiprofen axetil, compared to the group that only received tramadol at the end of surgery.¹⁸ However, the use of ropivacaine alone was not associated with an analgesic effect.¹²

Ketamine also belongs to the molecules whose local wound analgesic effect has been studied. The local ketamine analgesic effect is related to different mechanisms: blocking sodium, calcium, and potassium channels, as well as binding to opioid, cholinergic, D2, and 5-HT₂ receptors and monoamine transporters.^{9,19,20} It also decreases microglial activation and migration and prevents local inflammation extension and exacerbation through its action on the prototype inflammatory mediators, the adenosine receptor system, and the activation of the NMDA receptors.²¹ However, only a limited number of studies demonstrated the analgesic effect of ketamine in thyroid surgery, either locally or systemically.

In our study, ketamine (2 mg/kg) was injected into the wound after skin closure. It was associated with a significant reduction in VAS scores during swallowing compared to the saline solution group in PACU at 0, 10, and 20 minutes. In a prospective, controlled, double-blind, randomized study, Abd EL-Rahman *et al.*⁹ compared post-thyroidectomy analgesia in three different groups using local ketamine wound instillation, intramuscular ketamine injection, or placebo. He recorded that VAS scores at rest or during movement, as well as morphine consumption, were reduced in the local ketamine group compared to intramuscular ketamine and placebo. He then concluded that local ketamine instillation of 1 mg/kg of ketamine diluted in 10 ml of a saline solution was associated with a superior analgesic effect compared to the other groups. He also recorded that total morphine consumption and first analgesia demand were significantly lower in the local ketamine group.

We also demonstrated that local injection of ketamine significantly reduced the average morphine requirement compared to the saline solution group. The use of opioids can be associated with severe side effects such as nausea, vomiting, and respiratory distress.¹⁵ Thus, modern analgesic approaches aim to reduce both postoperative pain and opioid requirements.^{4,5}

Kim *et al.*²² also studied the effect of intravenous ketamine infusion during the bilateral axilla-breast approach for robotic or endoscopic thyroidectomy and concluded that it significantly reduced postoperative pain scores compared to the saline solution group with no increase in adverse effects. Lee *et al.*¹⁵ used ketamine infusion after robotic thyroidectomy and demonstrated that it was associated with a lower VAS score 24 hours after surgery and with a decrease in opioid needs.

The use of ketamine as a local wound infiltration agent was studied more frequently in oral, tonsillar, and abdominal surgeries. In their meta-analysis, Cho *et al.*²³ concluded that the use of ketamine locally or systematically could provide pain relief in children undergoing tonsillectomy without side effects. The addition of ketamine to ropivacaine for local tonsillar application was associated with better postoperative analgesia compared to the application of ropivacaine alone.²⁴ Dal *et al.*²⁵ proved that locally injected ketamine effectively reduced pain scores in patients undergoing adenotonsillectomy. However, in a recent prospect guideline for post-tonsillectomy pain management, Aldalmulij *et al.*²⁶ did not recommend the use of ketamine infiltration in children due to the risk of systemic side effects after absorption, although different studies consistently concluded that it was effective in reducing pain and analgesic requirements after tonsillectomy in children.

Infiltrating the surgical site using ketamine in pediatric patients undergoing cleft palate surgery was superior to Bupivacaine with respect to analgesic requirements, quality of sleep after surgery, and speed of recovery.²⁷ In third molar surgery, a meta-analysis based on prospective clinical trials and randomized controlled trials demonstrated the analgesic effect of local administration of ketamine and its anti-inflammatory potential during the first 24 hours.²⁸

Regarding abdominal surgeries, Honarmad *et al.*²⁹ conducted a randomized, double-blind, prospective, placebo-controlled study, and concluded that intravenous or subcutaneous infiltration prior to incision of 0.5 mg/kg of ketamine improved analgesia during the first six hours after appendectomy with no significant side effects. The same authors reported that subcutaneous ketamine infiltration or intravenous ketamine administration for patients undergoing open cholecystectomy before the surgical incision provided auxiliary analgesia 24 hours after surgery.

In a randomized double-blind study, patients undergoing cholecystectomy who received subcutaneous ketamine infiltration at a dose of 2 mg/kg or intravenous ketamine at a dose of 1 mg/kg 15 minutes before surgical incision reported enhanced analgesia for 24 hours after surgery.³⁰ The administered doses of ketamine varied in the literature within the range of 0.5 to 2 mg/kg.³¹ In our study, we infiltrated a solution containing 2 mg/kg ketamine based on established literature and clinical experience, in order to achieve effective analgesia while minimizing potential adverse effects.

Our study has several limitations. First, thyroid surgeries were performed by different surgeons. Second, we did not consider the size of the resected thyroid gland which can reflect the extent of surgery and influence postoperative pain.

Conclusions

In conclusion, local wound infiltration using 2 mg/kg of ketamine is an effective approach to reduce opioid requirements after thyroid surgery without increasing the side effects of ketamine.

Data availability

Underlying data

Figshare: Underlying data for 'Ketamine infiltration decreases opioid requirement after thyroid surgery', <https://doi.org/10.6084/m9.figshare.21365703.v1>.³²

This project contains the following underlying data:

- data ketamine thyroidectomy.sav (SPSS format; all datasets have been de-identified in accordance with the Safe Harbor method)
- CONSORT checklist

Data are available under the terms of the [Creative Commons Attribution 4.0 International Public Licence \(CC-BY 4.0\)](https://creativecommons.org/licenses/by/4.0/).

Acknowledgments

We would like to thank all nurses and the personnel of the operating unit, in the otolaryngology and anesthesiology departments for their assistance and cooperation.

References

1. Shih ML, Duh QY, Hsieh CB, *et al.*: **Bilateral superficial cervical plexus block combined with general anesthesia administered in thyroid operations.** *World J. Surg.* 2010; **34**(10): 2338–2343. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
2. Banasiewicz T, Meissner W, Pyda P, *et al.*: **Local anesthesia in thyroid surgery – Own experience and review of the literature.** *Pol. Przegl. Chir.* 2011; **83**(5): 264–270. [PubMed Abstract](#) | [Publisher Full Text](#)
3. Gan TJ: **Risk factors for postoperative nausea and vomiting.** *Anesth. Analg.* 2006; **102**(6): 1884–1898. [Publisher Full Text](#)
4. Motamed C, Merle JC, Yakhoul L, *et al.*: **Postoperative pain scores and analgesic requirements after thyroid surgery: comparison of three intraoperative opioid regimens.** *Int. J. Med. Sci.* 2006; **3**(1): 11–13.
5. Mayhew D, Sahgal N, Khirwadkar R, *et al.*: **Analgesic efficacy of bilateral superficial cervical plexus block for thyroid surgery: meta-analysis and systematic review.** *Br. J. Anaesth.* 2018; **120**(2): 241–251. [PubMed Abstract](#) | [Publisher Full Text](#)
6. Hoh SY, Doon YK, Chong SS, *et al.*: **Randomized controlled trial comparing bilateral superficial cervical plexus block and local wound infiltration for pain control in thyroid surgery.** *Asian J. Surg.* 2019; **42**(12): 1001–1008. [PubMed Abstract](#) | [Publisher Full Text](#)
7. Stamenkovic DM, Bezmarevic M, Bojic S, *et al.*: **Updates on Wound Infiltration Use for Postoperative Pain Management: A Narrative Review.** *J. Clin. Med.* 2021; **10**(20): 4659. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. Woldegerima YB, Hailekiros AG, Fitiwi GL: **The analgesic efficacy of bilateral superficial cervical plexus block for thyroid surgery under general anesthesia: a prospective cohort study.** *BMC. Res. Notes.* 2020; **13**(1): 42. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. Abd El-Rahman AM, El Sherif FA: **Efficacy of Postoperative Analgesia of Local Ketamine Wound Instillation Following Total Thyroidectomy: A Randomized, Double-blind, Controlled Clinical Trial.** *Clin. J. Pain.* 2018 Jan; **34**(1): 53–58. [PubMed Abstract](#) | [Publisher Full Text](#)
10. Sellami M, Feki S, Triki Z, *et al.*: **Bupivacaine wound infiltration reduces postoperative pain and analgesic requirement after thyroid surgery.** *Eur. Arch. Otorhinolaryngol.* 2018; **275**(5): 1265–1270. [PubMed Abstract](#) | [Publisher Full Text](#)
11. Loh JW, Taib NA, Cheong YT, *et al.*: **A Double-Blind, Randomized Controlled Trial of Pre-incision Wound Infiltration Using Diclofenac Versus Bupivacaine for Post-operative Pain Relief in Open Thyroid and Parathyroid Surgery.** *World J. Surg.* 2020; **44**(8): 2656–2666. [PubMed Abstract](#) | [Publisher Full Text](#)
12. Miu M, Royer C, Gaillat C, *et al.*: **Lack of Analgesic Effect Induced by Ropivacaine Wound Infiltration in Thyroid Surgery: A Randomized, Double-Blind, Placebo-Controlled Trial.** *Anesth. Analg.* 2016; **122**(2): 559–564. [PubMed Abstract](#) | [Publisher Full Text](#)

13. Zanos P, Moaddel R, Morris PJ, *et al.*: **Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms.** *Pharmacol. Rev.* 2018; **70**(3): 621–660.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
14. Gozal Y, Shapira SC, Gozal D, *et al.*: **Bupivacaine wound infiltration in thyroid surgery reduces postoperative pain and opioid demand.** *Acta Anaesthesiol. Scand.* 1994; **38**(8): 813–815.
[Publisher Full Text](#)
15. Lee J, Park HP, Jeong MH, *et al.*: **Efficacy of ketamine for postoperative pain management in robotic thyroidectomy: A prospective randomised study.** *J. Int. Med. Res.* 2018; **46**(3): 1109–1120.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. Dumlu EG, Tokaç M, Öcal H, *et al.*: **Local bupivacaine for postoperative pain management in thyroidectomized patients: A prospective and controlled clinical study.** *Ulus Cerrahi Derg.* 2015; **32**(3): 173–177.
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Jiang Y, Zhang Z, Liang B, *et al.*: **The effect of bupivacaine on postoperative pain following thyroidectomy: a systematic review and meta-analysis.** *Minerva Chir.* 2020; **75**(3): 193–202.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Li X, Yu L, Yang J, *et al.*: **Multimodal analgesia with ropivacaine wound infiltration and intravenous flurbiprofen axetil provides enhanced analgesic effects after radical thyroidectomy: a randomized controlled trial.** *BMC Anesthesiol.* 2019 Aug 31; **19**(1): 167. Erratum in: *BMC Anesthesiol.* 2019 Nov 13; **19**(1):210.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
19. Schnoebel R, Wolff M, Peters SC, *et al.*: **Ketamine impairs excitability in superficial dorsal horn neurones by blocking sodium and voltage-gated potassium currents.** *Br. J. Pharmacol.* 2005; **146**(6): 826–833.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Hayashi Y, Kawaji K, Sun L, *et al.*: **Microglial Ca(2+)-activated K(+) channels are possible molecular targets for the analgesic effects of S-ketamine on neuropathic pain.** *J. Neurosci.* 2011; **31**(48): 17370–17382.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. De Kock M, Loix S, Lavand'homme P: **Ketamine and peripheral inflammation.** *CNS Neurosci. Ther.* 2013; **19**(6): 403–410.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. Kim DH, Choi JY, Kim BG, *et al.*: **Prospective, randomized, and controlled trial on ketamine infusion during bilateral axillo-breast approach (BABA) robotic or endoscopic thyroidectomy: Effects on postoperative pain and recovery profiles: A consort compliant article.** *Medicine (Baltimore).* 2016; **95**(49): e5485.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Cho HK, Kim KW, Jeong YM, *et al.*: **Efficacy of ketamine in improving pain after tonsillectomy in children: meta-analysis.** *PLoS One.* 2014; **9**(6): e101259.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
24. Hong B, Lim CS, Kim YH, *et al.*: **Comparison of topical ropivacaine with and without ketamine on post-surgical pain in children undergoing tonsillectomy: a randomized controlled double-blind study.** *J. Anesth.* 2017; **31**(4): 559–564.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Dal D, Celebi N, Elvan EG, *et al.*: **The efficacy of intravenous or peritonsillar infiltration of ketamine for postoperative pain relief in children following adenotonsillectomy.** *Paediatr. Anaesth.* 2007; **17**(3): 263–269.
[Publisher Full Text](#)
26. Aldamluji N, Burgess A, Pogatzki-Zahn E, *et al.*: **PROSPECT Working Group collaborators*: PROSPECT guideline for tonsillectomy: systematic review and procedure-specific postoperative pain management recommendations.** *Anaesthesia.* 2021; **76**(7): 947–961.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. Jha AK, Bhardwaj N, Yaddanapudi S, *et al.*: **A randomized study of surgical site infiltration with bupivacaine or ketamine for pain relief in children following cleft palate repair.** *Paediatr. Anaesth.* 2013; **23**(5): 401–406.
[Publisher Full Text](#)
28. Esparza-Villalpando V, Ascencio-Padilla R, Pozos-Guillen A, *et al.*: **Local Ketamine Improves Postoperative Analgesia After Third Molar Surgery.** *J. Oral Maxillofac. Surg.* 2019; **77**(12): 2386–2400.
[PubMed Abstract](#) | [Publisher Full Text](#)
29. Honarmand A, Safavi M, Karaky H: **Preincisional administration of intravenous or subcutaneous infiltration of low-dose ketamine suppresses postoperative pain after appendectomy.** *J. Pain Res.* 2012; **5**: 1–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Safavi M, Honarmand A, Nematollahy Z: **Pre-incisional analgesia with intravenous or subcutaneous infiltration of ketamine reduces postoperative pain in patients after open cholecystectomy: a randomized, double-blind, placebo-controlled study.** *Pain Med.* Sept 2011; **12**(9): 1418–1426.
[PubMed Abstract](#) | [Publisher Full Text](#)
31. Bai JW, An D, Perlas A, *et al.*: **Adjuncts to local anesthetic wound infiltration for postoperative analgesia: a systematic review.** *Reg. Anesth. Pain Med.* 2020 Aug; **45**(8): 645–655.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Sellami M: **Underlying data for 'Ketamine infiltration decreases opioid requirement after thyroid surgery'.**
[Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:   

Version 2

Reviewer Report 01 February 2024

<https://doi.org/10.5256/f1000research.154754.r235357>

© 2024 Minh P. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Pham Quang Minh

Hanoi Medical University, Hanoi, Vietnam

1. The study design:

- Random grouping is unequal: The proportion of patients undergoing total thyroidectomy or partial thyroidectomy is much different between the two groups. Different types of surgery result in different level of pain. It make great influence on research results.
- The post-operative pain relief design is not appropriate. When VAS score > 30, author used Nefopam. Nefopam is a strong pain relief but it causes a tachycardia so it needs to be infused slowly, with an infusion time is 30 minutes or more. So, this medicine is not suitable for pain relief. An NSAID group such as Ketorolac can be used. Furthermore, when using Nefopam, the dose must also be controlled, not exceeding 120mg per day. So if the patient has already taken 120 mg and still has pain, what is the next treatment?
- Patients were assessed for pain both at rest or swallowing, but when swallowing, the VAS score was very high in the group not using Ketamine. This is not clinically appropriate in the first 120 minutes, because when author knew the patients were in pain, author still force the patient to perform swallowing for research without giving any additional pain relief. It can be said that author did not respect research ethics.

2. Data results

- It need to add a table of results about side effects of pain relief methods, especially hallucinations when using Ketamine. The research object and method section should clearly state: Criteria for diagnosing hallucinations, prevention and treatment.

3. Discussion and conclusion

- Discussion does not focus on the question research or the research results.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anesthesiologist

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 04 September 2023

<https://doi.org/10.5256/f1000research.154754.r197863>

© 2023 Romdhani C et al. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Chihebeddine Romdhani 

¹ Research Unit UR17DN05, Military Hospital of Tunis, Tunis, Tunisia

² Faculty of Medicine of Tunis, Universite de Tunis El Manar, Tunis, Tunisia, Tunisia

Widd Kaabi

Faculty of Medicine of Tunis, Universite de Tunis El Manar, Tunis, Tunisia, Tunisia

The authors have addressed the requested revisions.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Regional anesthesia, Anesthesiology, critical care, cardiac anesthesia, artificial intelligence

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 10 August 2023

<https://doi.org/10.5256/f1000research.140082.r187838>

© 2023 Kahloul M. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Mohamed Kahloul

Department of Anesthesia and Intensive Care, Sahloul Academic Hospital, Faculty of Medicine of Sousse, University of Sousse, Sousse, Sousse, Tunisia

Title:

- Postoperative opioid requirements were assessed only in the PACU. Postoperative pain is your primary outcome. Please rephrase your title.

Methods:

- Difficult airways should be considered as an exclusion criteria because you had assessed VAS during swallowing.
- Please precisely include which ketamine concentration was used.

Results:

- Baseline characteristics should be comparable between the two groups. Please verify your data (age, performed surgery).
- You have many VAS assessments exceeding 3/10. What was your rescue analgesia?

Discussion:

- The choice of ketamine dosage should be discussed.

- "However, the use of ropivacaine was not associated with an analgesic effect.¹²" Others studies had found different results and they should be considered¹.
- VAS was considered as a limitation while it is a validated tool.

Conclusion:

- Please put "to reduce" instead of "to reducing".

References

1. Wang N, Zhang J, Ming J: Benefits of ropivacaine infiltration for reducing postoperative pain after thyroid surgery: a meta-analysis of randomized controlled trials. *Int J Clin Exp Med*. 2019; **12** (6). [Reference Source](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anesthesia and intensive care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 17 Aug 2023

Moncef Sellami

We express our gratitude to the reviewer for his meticulous assessment, which has contributed significantly to the refinement of our study.

Title:

- Postoperative opioid requirements were assessed only in the PACU. Postoperative pain is your primary outcome. Please rephrase your title.

Author response: The title has been revised as 'Ketamine infiltration improves analgesia after thyroid surgery'.

Methods:

- Difficult airways should be considered as an exclusion criteria because you had assessed VAS during swallowing.
- Please precisely include which ketamine concentration was used.

Author response:

- **In effect, difficult airways were considered an exclusion criterion.**
- **We specified the ketamine concentration used, which was 50mg/ml**

Results:

- Baseline characteristics should be comparable between the two groups. Please verify your data (age, performed surgery).
- You have many VAS assessments exceeding 3/10. What was your rescue analgesia?

Author response:

- **The patients were randomized and the results were statistically verified.**
- **Our data, including age and type of surgery, have been carefully validated.**
- **We specified that the rescue analgesic during hospitalization was Nefopam in the case of VAS values greater than 30**

Discussion :

- The choice of ketamine dosage should be discussed.

Author response:

In our study, we infiltrated a solution containing 2 mg/kg ketamine based on established literature and clinical experience, in order to achieve effective analgesia while minimizing potential adverse effects.

We discuss the chosen dose.

- "However, the use of ropivacaine was not associated with an analgesic effect.¹²"
Others studies had found different results and they should be considered¹.

Author response:

We discussed this issue and reported the study by Li X et al.

- VAS was considered as a limitation while it is a validated tool.

Author response:

We have considered the reviewer's comment and revised the limitations section of the study. Indeed, the VAS is a validated tool despite its subjective nature.

Conclusion:

- Please put "to reduce" instead of "to reducing".

Author response:

We have made the requested change, replacing "to reducing" with "to reduce" in the relevant section.

Competing Interests: No competing interests were disclosed.

Reviewer Report 31 July 2023

<https://doi.org/10.5256/f1000research.140082.r187834>

© 2023 Romdhani C et al. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Chihebeddine Romdhani 

¹ Research Unit UR17DN05, Military Hospital of Tunis, Tunis, Tunisia

² Faculty of Medicine of Tunis, Universite de Tunis El Manar, Tunis, Tunisia

Widd Kaabi

Faculty of Medicine of Tunis, Universite de Tunis El Manar, Tunis, Tunisia

In this study, researchers investigated the effects of local ketamine wound infiltration versus saline placebo on postoperative pain and opioid consumption in patients undergoing thyroid surgery. After randomizing 64 patients to receive either ketamine or saline infiltration, the researchers found that the ketamine group had lower VAS pain scores during the PACU stay for static pain at rest and dynamic pain on swallowing. The ketamine group consumed significantly less morphine in the PACU than the saline group. No adverse effects were reported. The authors concluded that local ketamine can reduce postoperative opioid use without increasing side effects. This study is well-designed and addresses an important clinical question.

We recommend you to :

- Provide more details regarding the randomization process: Was a computer random number generator used? Were block randomization or stratification techniques used?
- Presenting VAS scores graphically could better visualize trends.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Regional anesthesia, Anesthesiology, critical care, cardiac anesthesia, artificial intelligence

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 17 Aug 2023

Moncef Sellami

We thank reviewers for the quality and relevance of the feedback.

In this study, researchers investigated the effects of local ketamine wound infiltration versus saline placebo on postoperative pain and opioid consumption in patients undergoing thyroid surgery. After randomizing 64 patients to receive either ketamine or saline infiltration, the researchers found that the ketamine group had lower VAS pain scores during the PACU stay for static pain at rest and dynamic pain on swallowing. The ketamine group consumed significantly less morphine in the PACU than the saline group. No adverse effects were reported. The authors concluded that local ketamine can reduce postoperative opioid use without increasing side effects. This study is well-designed and addresses an important clinical question.

We recommend you to :

Provide more details regarding the randomization process: Was a computer random number generator used? Were block randomization or stratification techniques used?

Author response:

The patients were randomly assigned to the two groups through an online random list generator (<https://www.random.org>), ensuring an unbiased allocation. The randomization method was specified.

Presenting VAS scores graphically could better visualize trends.

Author response:

Although we appreciate the suggestion to present VAS scores graphically, we found that tabulated data provide a more precise and interpretable representation in this particular context.

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research