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Chapter

Low-Dose Ketamine for Acute Postoperative Pain Treatment

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Abstract

Treatment of acute postoperative pain is an essential part of perioperative care and if left untreated could complicate the healing period. Ketamine blocks nociceptive pain and pain arising from inflammation. Therefore, it is potentially beneficial in the postoperative period. After systematic review using "MEDLINE/PubMed (NLM)" database, we analyzed 18 studies published during 2011–2020 and found that 0.5 mg/kg/h ketamine bolus and 0.1–0.25 mg/kg/h ketamine infusion to be the most effective dose to alleviate postoperative acute pain. Ketamine, when compared with a placebo, did not have any impact on patients' satisfaction with postoperative pain management and overall well-being. Only three studies revealed more frequent adverse reactions to ketamine after surgery suggesting that ketamine did not have any impact on patients' postoperational rehabilitation. So, it is the option to recommend low-dose ketamine to be part of multimodal analgesia in acute severe postoperative pain treatment. It can be used in both opioid-dependent and opioid-tolerant patients. Ketamine bolus should be ≤0.35 mg/kg and infusion ≤1 mg/kg/h. One should avoid the use of ketamine in pregnant women, people with cardiovascular diseases, acute psychosis, impaired liver function, increased intracranial, and intraocular pressure. Intranasal ketamine may be considered for children during procedures outside of the operation room.

Keywords: low dose, ketamine, acute pain management

1. Introduction

Treatment of acute postoperative pain is an important part of perioperative care. Insufficient analgesia is related to adverse outcomes such as immunosuppression, hyperglycemia, aggravated early rehabilitation, deterioration in patients' quality of life, more common postoperative complications, a longer period of recovery after surgery, and progress from acute to chronic pain [1, 2].

Ketamine, a *N*-methyl-D-aspartate (NMDA) receptor antagonist, is a cheap and potentially opioid-sparing effect having drug, which in recent years attains more recognition for multimodal pain management [1, 3, 4]. NMDA receptors are related to nociceptive pain and pain arising from inflammation [5]. Blocking those receptors may contribute to the effectiveness of opioids and lower the prevalence of chronic pain syndrome [1, 4]. An adverse side effect of ketamine is dose-dependent and could be avoided by using anxiolytics for premedication, selecting patients more carefully before the operation, using antihypertensive drugs together with ketamine infusion [3].

U.S. Food and Drug Administration indications for the usage of ketamine are adjuvant to general anesthesia, induction agent for general anesthesia, sedation for short-time procedures [6]. This means that usage of ketamine for acute postoperative pain treatment is not based on official indications, because there is a lack of researches on this topic.

In recent years, there has been considerable interest in ketamine efficiency in treating acute postoperative pain. Guidelines published in 2018 indicate that a regimen of low-dose ketamine can be described as following—ketamine bolus lower than 0.35 mg/kg, infusion—lower than 1 mg/kg/h [5]. In 2015, Jouguelet-Lacoste with colleagues published a literature review that included five meta-analyses studying intravenous ketamine impact on postoperative pain inhibition. They revealed that ketamine lowers pain points and additional opioid consumption. Four out of five researches revealed that pain scores in the first 24 hours after operation lowered 87.5, 59, 54.5, and 25% compared to placebo [7]. In 2018, Cochrane systematic review included 130 pieces of research to find if low-dose ketamine effectively alleviates acute postoperative pain. Consumption of opioids in the first 24 hours was 8 mg less and the first 48 hours 13 mg less when compared with placebo. Pain at rest lowered 5/100 mm of visual analog scale (VAS), during movement 6/100 mm VAS in the first 48 hours [8].

Unfortunately, there were no guidelines on what dosage, which patient group, and in what way ketamine should be used. In 2018, the American Society of Regional Anesthesia and Pain Medicine together with the American Academy of Pain Medicine and the American Society of Anesthesiologists published guidelines on intravenous usage of ketamine for managing acute pain. They indicated the most suitable group of patients for using ketamine, its dosage, indications, contraindications, and trials supporting this evidence. The authors of these guidelines also pointed out that more trials should be done to determine the accurate and effective doses of ketamine for effective acute pain management [6].

2. Methods

The design of this systematic review of the literature is followed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. Data were identified from searches of MEDLINE (PubMed) database. The combination of keywords included terms “low” and “dose” and “ketamine” and “pain” and “postoperative” in PubMed Advanced Search Builder in all fields accordance with the PICO criteria: “Participants” were limited to 18 years and older, “interventions” covered were randomized controlled clinical trials on low-dose intravenous ketamine, “comparator”—comparing ketamine with placebo and/or a different dose of ketamine, and “outcomes” discovered after a thorough analysis of researches and classified according to the trial type and most common findings. Records were screened by the title, abstract, and full text. Inclusion criteria were as follows: (1) full-text articles published in English; (2) not older than 2011; (3) double- or triple-blinded randomized prospective trials of different ketamine intravenous dosage and/or placebo; (4) American Society of Anesthesiologists (ASA) I–III class; (5) age over 18 years; (6) VAS or Numeric Pain Scale (NPS) used for evaluation of acute postoperative pain. However, review or meta-analysis or systematic review articles, commentaries, abstract-only publications, guidelines, case reports, not randomized trials, ketamine given intramuscularly/orally/subcutaneous, ketamine given in the emergency department were excluded. The detailed search flowchart is presented in **Figure 1**.

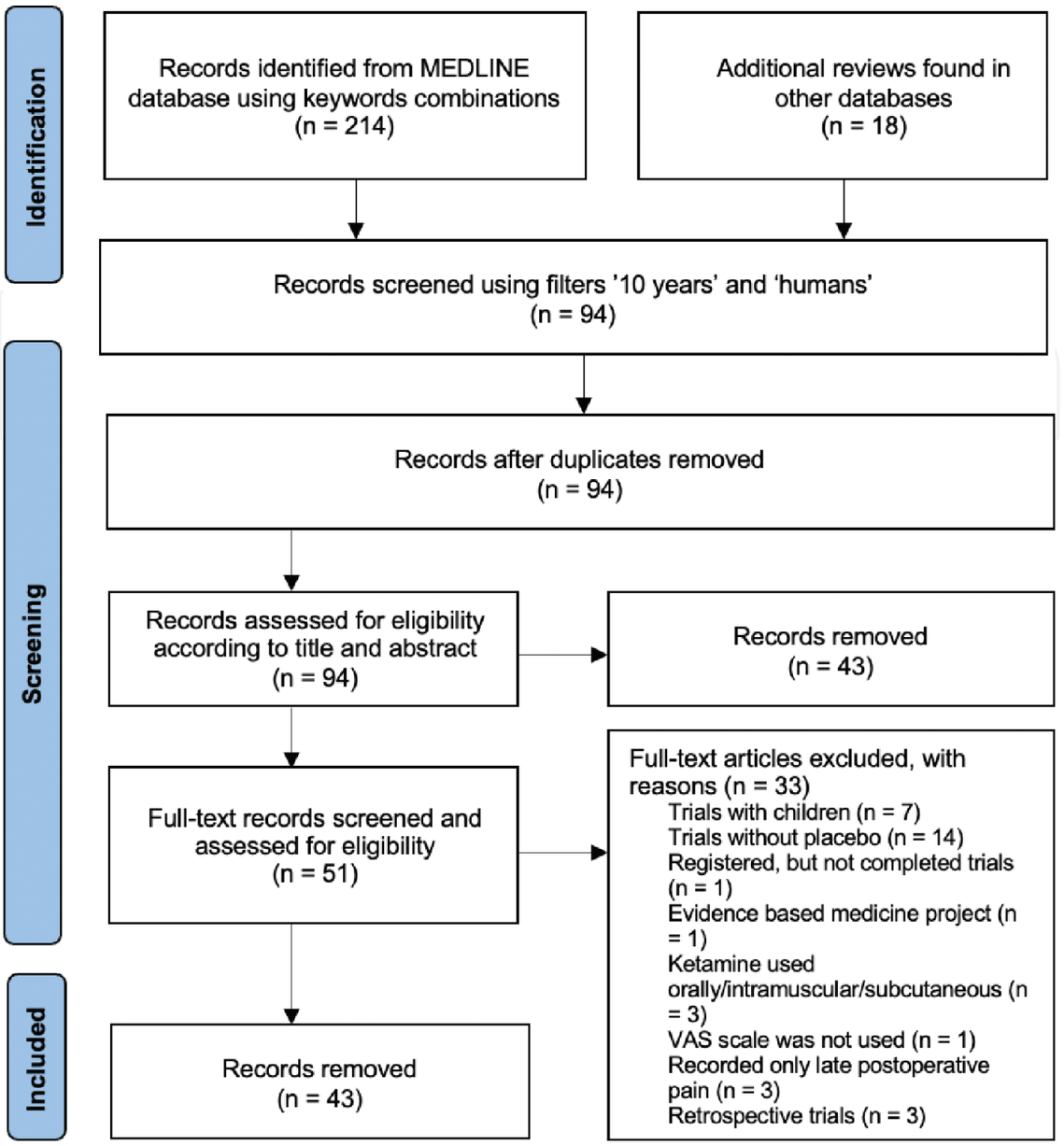

Figure 1.
Flowchart.

3. Results

3.1 Study selection process

The research yielded 214 results, extracted from one database. All duplicates were removed, and 94 articles were checked manually for relevance by screening their titles and abstracts. About 51 results met the inclusion criteria, but only 18 were included after a full-text review. Only full-text articles were selected because the information given in the abstract was not sufficient for the thorough analysis. The randomized trials, conducted in 2011–2020 and which compared different doses of ketamine and placebo given for patients during various surgeries to investigate the effect of the drug on the management of acute postoperative pain, were analyzed. About 33 publications were excluded for reasons explained in **Figure 1**.

3.2 Characteristics of included studies

Those 18 selected trials could be divided into several groups—those who investigate ketamine bolus dose (six trials), those who investigate different infusion dose peri- and postoperation (two trials), those who investigate both only during operation (six trials), and those who investigate bolus and infusion, which is continued during and after the operation (four trials). A summary of the results of 18 analyzed studies is provided in **Table 1**.

3.3 Synthesis of results

All 18 trials (bolus/infusion/both) included in this systematic review were investigated and compared in three categories—pain, overall satisfaction, and adverse reactions (AR). The summarized results can be seen in **Table 2**.

Subramaniam and colleagues [9] conducted a trial wanting to find out ketamine impact on pain management after laminectomy. Pain scores remained high despite analgesic therapy with ketamine, epidural bupivacaine, PCA with hydromorphone, and other adjuvants. No adverse reactions in the ketamine group were observed. Meanwhile, Kim with fellow authors [19] conducted a similar trial, but in PCA, they used fentanyl. Their research revealed that 0.5 mg/kg ketamine bolus and 2 μg/kg/min ketamine infusion statistically significantly lower fentanyl doses in the first 48 hours after surgery without more frequent adverse reactions. In both trials, pain evaluation in points did not differ.

Chumbley with colleagues' [24] trial revealed that 0.1 mg/kg IV ketamine bolus and 0.1 mg/kg/h infusion, started 10 min before thoracotomy, lowers consumption of opioids and pain scores at 48 h after surgery.

Yazigi with co-authors [18] injected IV 0.1 mg/kg ketamine bolus before the surgery and IV ketamine infusion of 0.05 mg/kg was continued for 72 hours after lobectomy during thoracotomy, same as bupivacaine that was injected through the intercostal catheter for 72 hours. Ketamine did not have any significant difference in pain scores, additional morphine consumption, sedation, and other adverse psychomimetic effects.

Parikh with other scientists [10] aimed to find out the efficiency of pain management by using ketamine for patients after open renal surgery. They favored the use of ketamine, as its bolus and infusion started after anesthesia induction which reduced pain scores in the first 12 hours, reduced or delayed the use of additional postoperative morphine, and does not cause a more frequent adverse reaction.

Kaur and colleagues [22] discovered that ketamine bolus and infusion were given only during surgery lowered pain scores in the first 6 hours, reduced opioid consumption, and did not have an adverse effect on patients after cholecystectomy.

Nielsen with co-authors [14] investigated opioid-dependent patients' pain management with ketamine bolus and infusion after back surgery. They did not find any difference in pain scores during 2–24 hours after surgery, but morphine consumption in the PCA in the first 24 hours was significantly lower in the research group. No statistical significance was observed on patients' overall satisfaction and adverse reaction rate.

Haliloglu with colleagues [23] researched ketamine bolus and infusion during C-section. Their trial revealed that ketamine reduced postoperative PCA morphine consumption in the first 24 hours, but it did not reduce pain scores in the research group in all hours except for the first 15 min after surgery.

Ates with others [26] injected ketamine bolus and infusion during septorhinoplasty and discovered that it reduces pain scores at every hour and lowers additional

Author	Year of publishing, country	Surgery type	Number of patients	Type of anesthesia	Inclusion criteria	Pain and satisfaction evaluation
Subramaniam [9]	2011, USA	Lumbar/thoracic laminectomy	30	General anesthesia	Age 18 and older, ASA 1–3 class	VAS (0–10 cm) at 0, 1, 2, 4, 8, 12, 18, 24, 36, 48 h after surgery. Satisfaction on pain management at 48 h (1 p. bad, 10 p. good)
Parikh [10]	2011, India	Open renal surgery	60	General anesthesia	Age 18–70, ASA 1–2 class	VAS (0–10 cm) every 15 min at the first hour, and then at 4, 8, 12, 16, and 24 h after surgery
Bilgen [11]	2012, Turkey	C-section	140	General anesthesia	ASA 1–2 class, primiparas with an indication for C-section	NPS (0–10 p.) at 2, 6, 18, 24, 48 h after surgery
Mendola [12]	2012, Italy	Muscle-sparing posterolateral thoracotomy	62	General and epidural anesthesia	ASA 1–3 class	NPS (0–10 p.) at 1, 2, 4, 12, 18, 24 h and every 6 h following 3 days after surgery and 2 times a day until discharge
Song [13]	2013, Korea	1–2 level posterior lumbar fusion	50	General anesthesia	ASA 1–2 class, non-smoking women, age 20–65, with a risk for postoperative nausea and vomiting	VAS (0–100 mm) at 30 min, 6, 12, 24, 36, 48 h after surgery at rest and movement
Nielsen [14]	2017, Denmark	1–2 level middle lumbar fusion	147	General anesthesia	Chronic back pain for >3 months, age 18–85, ASA 1–3 class, BMI 18–40 kg/m^2, opioid usage for >6 months	VAS (0–100 mm) at 2, 6, 12, 18, 25 h after surgery at rest ant movement
Honarmand [15]	2011, Iran	Appendectomy	90	General anesthesia	ASA 1–2 class, age 18–60, no abscess or perforation	VAS (0–10 cm) at 0, 10, 20, 30 min, 6–12–18–24 h after surgery.
Menkiti [16]	2012, Nigeria	C-section	56	General anesthesia	ASA 1–2 class, age 18–60, no abscess or perforation	VAS (0–10 cm) at 0, 10, 20, 30 min, 6–12–18–24 h after surgery.
Nesek-Adam [17]	2012, Croatia	Laparoscopic cholecystectomy	80	General anesthesia	ASA 1–2 class, age 18–70	VAS (0–10 cm) and numeric pain scale (0–4 p.) 0, 1, 2, 4, 6, 12, 24 h after the surgery. Overall satisfaction evaluated after 24 h (1–5 p.)

Author	Year of publishing, country	Surgery type	Number of patients	Type of anesthesia	Inclusion criteria	Pain and satisfaction evaluation
Yazigi [18]	2012, Lebanon	Lobectomy during posterior dorsal thoracotomy, while having lung cancer	60	General anesthesia and intercostal nerve block	ASA 2–3 class	VAS (0–100 mm) 1, 6 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72 h after the surgery. Ramsav sedation scale (1–6 p.)
Kim [19]	2013, Korea	Posterior decompression and posterior lumbar spinal cord surgery	60	General anesthesia	ASA 1–2 class	VAS (0–100 mm) 1, 6, 24, 48 h after the surgery and movement. Overall satisfaction evaluated after 48 h (1–5 p.)
Han [20]	2013, Korea	C-section	36	Spinal anesthesia	ASA 1–2 class, between 37 and 42 weeks of pregnancy	VAS (0–10) 2, 6, 24, 48 h after the surgery at a rest and while coughing Overall satisfaction evaluated after 48 h (1–5 p.)
Rahmanian [21]	2015, Iran	C-section	160	Spinal anesthesia	Singleton pregnancy	Numeric pain scale (0–10 p.) 1, 2, 6, 12 h after the surgery
Kaur [22]	2015, India	Open cholecystectomy	80	General anesthesia	ASA 1–2 class	VAS (0–100 mm) 0, 2, 4, 6, 12, 24 h after the surgery. Overall satisfaction evaluated after 24 h (1–5 p.) Nausea and sedation evaluation (0–3 p.)
Haliloglu [23]	2016, Turkey	C-section	52	General anesthesia	ASA 1–2 class	Numeric pain scale (0–10 p.) 15 min, 2, 6, 12, 18, 24 h after the surgery
Chumbley [24]	2019, UK	Thoracotomy	70	Not specified	≥18 years, able to read English	Numeric pain scale (0–10 p.) 24, 48 h after the surgery at a rest and while coughing
Boenigk [25]	2019, USA	Two or more levels of lumbar spinal cord surgery	124	General anesthesia	ASA 1–3 class	Numeric pain scale (0–10 p.) 0, 30 min. 1, 1. 5, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 h after the surgery
Ates [26]	2020, Turkey	Septorhinoplasty	48	General anesthesia	ASA 1–2 class	VAS (0–10 cm) 0, 1, 2, 4, 8, 12, 24 h after the surgery. Overall satisfaction is evaluated (1–5 p.)

Table 1.
Descriptive characteristics of the different trials which researched ketamine's bolus, infusion, or both.

Author	Research group (RG)	Control/other group (CG)	Postoperative pain management	Results			
				Pain	Overall satisfaction	Adverse reaction	Overall
Bolus and infusion during and after surgery							
Subramaniam	Intravenous (IV) ketamine bolus 0.15 mg/kg for induction and continuous infusion at 2 μg/kg/min during and after surgery for 24 h	Same scheme, but instead of ketamine IV NaCl 0.9%	Patient-controlled analgesia (PCA)—hydromorphone 0.125 boluses every 5 min (max 1.25 mg/h). Epidural block with bupivacaine. Nausea and vomiting—IV ondansetron 4 mg.	Not statistically significant	Not statistically significant	Not statistically significant, the control group experienced nausea and AR-related to central nervous system (CNS) more often	—
Kim	RG1—IV 1 μg/kg/min ketamine infusion started before incision and continued for 48 h and 0.5 mg/kg ketamine bolus/// RG2—same scheme, but infusion at 2 μg/kg/min and bolus 0.5 mg/kg	Same scheme, but instead of ketamine—IV NaCl 0.9%	PCA with fentanyl—15 μg bolus max every 5 min. Nausea or vomiting—IV 10 mg metoclopramide/4 mg ondansetron.	RG2 used less fentanyl than CG and RG1 ($p < 0.05$). VAS—not statistically significant	Same results among the group	No one had hallucinations or nightmares. Other things—not statistically significant	+
Chumbley	IV 0.1 mg/kg ketamine bolus 10 min before surgery and IV 0.1 μg/kg/h ketamine infusion for 96 h	Same scheme, but instead of ketamine—unknown placebo	Differ—thoracic epidural infusion/ PCA ± paravertebral infusion of a local anesthetic	NPC 48 h after surgery lower in RG ($p = 0.03$). RG consumed less opioids at 24 and 48 h	Not examined	RG had vivid dreams and felt weaker than CG ($p = 0.001$ and $p = 0.02$). Nausea, vomiting, rash, and sedation did not differ.	+

Author	Research group (RG)	Control/other group (CG)	Postoperative pain management	Results			
				Pain	Overall satisfaction	Adverse reaction	Overall
Yazigi	Before the incision IV 0.1 mg/kg ketamine bolus IV 0.05 mg/kg/h ketamine infusion for 72 h	Same scheme, but instead of ketamine—IV NaCl 0.9%	72 h after the surgery—1 mg/mL 0.1 mL/kg/h bupivacaine through intercostal catheter. Also IV 1 g paracetamol, 50 mg ketoprofen every 6 h. If VAS > 40 mm—morphine sulfate titrated 2 mg bolus max every 5 min, max dose 0.1 mg/kg/h	No statistical difference—while coughing (p = 0.7), while at rest (p = 0.75)	Not examined	Not statistically significant for sedation, dizziness, nausea, or vomiting. For two patients in RG had hallucinations, impaired vision, or nightmares.	—
Bolus and infusion only during surgery							
Parikh	After the induction IV 10 mL (1 mg/mL–0.15 mg/kg) ketamine bolus and 50 mL (1 mg/mL–0.12 mL/kg/h-2 μg/kg/min) infusion until the end of the surgery	Same scheme, but instead of ketamine—IV NaCl 0.9%	When VAS > 40 - > morphine 1 mg	In the first 12 h after the surgery VAS was lower in the RG. In RG 5 patients needed an additional analgesic, in CG all patients needed it so morphine consumption at RG was lower than in the KG.	Not examined	Four patients in RG felt nausea or vomiting.	+
Nielsen	IV 0.5 mg/kg S-ketamine bolus after the induction and IV 0.25 mg/kg ketamine infusion until the last stich	Same scheme, but instead of ketamine—IV NaCl 0.9%	For everyone in the first 24 h—1 g paracetamol, orally every 6 h started from the 2nd h. PCA with 2.5 mg morphine boluses max every 5 min. For nausea or vomiting IV 4 mg ondansetron - > if not effective—droperidol	No statistical difference—when moving (p = 0.63) and at the rest (p = 0.62) at 2–24 h. RG used less morphine (p < 0.001).	Not statistically significant	Not statistically significant, but vomiting less frequent in the RG at 0–24 h.	+

Author	Research group (RG)	Control/other group (CG)	Postoperative pain management	Results			
				Pain	Overall satisfaction	Adverse reaction	Overall
Haliloglu	At induction IV 0.5 mg/kg ketamine bolus and infusion 0.25 mg/kg/h until the end of operation	Same scheme, but instead of ketamine—IV NaCl 0.9%	NPS >4 in the recovery room - > 0.05 mg/kg morphine. PCA 0.5 mg/kg morphine at 1 mg boluses max every 10 min. If PCA not efficient—IV 75 mg diclofenac.	15 min after the surgery NPS lower in the RG (p = 0.001) at 2, 6, 12, 18, 24 h—did not differ (p > 0.05). Consumption of morphine 0–24 h was lower in the RG (p = 0.001)	Not examined	Spontaneous, involuntary eye movement, hallucinations, and dual vision did not occur to anyone. Most patients experienced nausea, vomiting, and itching, but no statistical difference (p > 0.05).	+
Kaur	IV 0.2 mg/kg ketamine bolus and infusion 0.1 mg/kg/h until the end of operation	Same scheme, but instead of ketamine—IV NaCl 0.9%	VAS >30 mm—IV 0.05 mg/kg morphine bolus. Medium and strong nausea–IV 0.1 mg/kg ondansetron	During the first 6 h, VAS was lower in the RG (p < 0.05), but not different at 12 and 24 h. RG patients needed less additional analgesic (p = 0.001). The usage of morphine was lower in the RG (p = 0.001).	Not statistically significant	No one experienced hallucinations, sedation, headache, dizziness, breathing disorder. Nausea and vomiting were similar, but statistically not different.	+
Ates	At induction IV 0.5 mg/kg ketamine bolus and 0.25 mg/kg/h infusion continued during operation	Same scheme, but instead of ketamine—IV NaCl 0.9%	For everyone at 12 and 24 h after the surgery—50 mg dexketoprofen. If VAS ≥ 4–1 mg/kg tramadol.	VAS was greater in the CG at 30 min. 1, 2, 4, 8, 12, 24 h (p < 0.05). CG needed more additional analgesics than RG (p = 0.022)	Higher in the RG (p = 0.003)	Nausea was more intense in the CG, but not statistically. RG did not experience hallucinations, arrhythmias, or vomiting.	+
Han	IV 0.5 mg/kg ketamine bolus and infusion 0.25 mg/kg/h during surgery	Same scheme, but instead of ketamine—IV NaCl 0.9%	PCA with 25 μg/mL fentanyl—as needed, max every 15 min. If VAS ≥ 5 or patient request—intramuscular 30 mg ketorolac.	At 2 h RG used less fentanyl (p = 0.033), but there was no difference at 6, 24, 48 h. VAS—not statistically significant.	Not statistically significant.	No one experienced hallucinations or nightmares.	—

Author	Research group (RG)	Control/other group (CG)	Postoperative pain management	Results			
				Pain	Overall satisfaction	Adverse reaction	Overall
Bolus							
Bilgen	Before the induction IV: RG1—ketamine 0.25 mg/kg; RG2—ketamine 0.5 mg/kg; RG3—ketamine 1 mg/kg bolus.	Same scheme, but instead of ketamine—IV NaCl 0.9%	PCA for 48 h after the surgery - > morphine chloride 0.5 mg/mL - > 1 mg bolus every 10 min. If needed—IV 75 mg diclofenac every 12 h. If NPS > 4, additional IV morphine 0.005 mg/kg.	No statistical difference (p = 0.2–0.9)	Not examined	No statistical difference (p = 0.3–0.7). In RG1—2 felt nausea, in RG2—3 felt nausea, 1 vomited and 1 experienced hallucination, in RG3—4 had spontaneous, involuntary eye movement, 1 vomited and had an occurrence of dual sight, in the CG—1 felt nausea and 1 experienced spontaneous, involuntary eye movement.	—
Song	After induction IV 0.3 mg/kg ketamine bolus + PCA (fentanyl 20 μg/kg, ondansetron 9 mg, ketamine 3 mg/kg)	Same scheme, but instead of ketamine—IV NaCl 0.9%	PCA and 25 mg meperidine, when VAS > 40 mm or if the patient asks. When nausea >6 points (in the system of 10 points, 0—no nausea, 10 strong and unbearable nausea) or if a patient asks—IV 4 mg ondansetron	No statistical difference—when moving or at the rest. RG used less fentanyl 48 h after the surgery (p = 0.035, 773 and 957 μg)	Not examined	RG felt nausea more common than CG at 0–6 h (p = 0.016). RG experienced dizziness in the first 48 h (p = 0.047). Three patients experienced hallucination/nightmares and dysphoria in the RG.	+

Author	Research group (RG)	Control/other group (CG)	Postoperative pain management	Results			
				Pain	Overall satisfaction	Adverse reaction	Overall
Honarmandt	IV 0.5 mg/kg 3 mL ketamine 15 min before the incision	Subcutaneous 0.5 mg/kg 3 mL ketamine/// subcutaneous infiltration of NaCI 0.9% 3 mL 15 min before the incision	If VAS > 4 cm—IV 0.4 mg/kg meperidine - > if it does not help in 10 min - > 0.2 mg/kg. Do not exceed 2 mg/kg in 4 h. Nausea >10 min. –0.1 mg/kg metroclopramide IV - > if needed, repeat after 1 h.	VAS scores were lower at 10, 20, 30 min in ketamine groups ($p < 0.05$) but did not differ between them. When comparing CG and RG groups at 6, 12, 18, 24 h VAS were lower in RG ($p < 0.05$). At 12, 18, 24 h VAS were lower in RG when compared with subcutaneous ketamine ($p < 0.05$)	Not examined	Sedation did not differ. AR did not differ, no one had delirium, hallucinations, or nightmares.	+
Menkiti	IV 0.15 mg/kg 2 mL ketamine bolus after spinal anesthesia	Same scheme, but instead of ketamine—IV NaCl 0.9%	If VAS >3 IV 75 mg diclofenac. If it does not help - > 30 mg pentazocine 0, every 4 h and 75 mg diclofenac every 8 h if needed.	CG VAS was bigger at 60, 90, 120 min. Statistically significant VAS > 3 p. differed at 90, 120, 150 min. RG received less analgesic after the surgery ($p < 0.001$)	Not examined	No significant difference, usually hypotension, trembling.	+

Author	Research group (RG)	Control/other group (CG)	Postoperative pain management	Results			
				Pain	Overall satisfaction	Adverse reaction	Overall
Adam	IV 100 mL NaCl 0.9% 20 min. Before anesthesia and 0.15 mg/kg 5 mL IV ketamine before incision///IV 1 mg/kg diclofenac in 100 mL NaCl 0.9% 20 min before anesthesia and 5 mL IV NaCl 0.9% before incision///IV 1 mg/kg diclofenac in 100 mL NaCl 0.9% 20 min before anesthesia and IV 0.15 mg/kg 5 mL ketamine before incision	IV 100 mL NaCl 0.9% 20 min before anesthesia and 5 mL IV NaCl 0.9% before incision	If VAS > 4—diclofenac IV. If no effect—IV 1.25 g metamizole and IV 100 mg tramadol in 100 mL 0.9% NaCl per 20 min.	VAS max 1 h after surgery. Ketamine and diclofenac group pain scores lower than CG at 1, 2, 4, 6 h and lower than ketamine group at 1, 2 h. During the first 6 h, pain scores were higher in CG rather than the ketamine and diclofenac group. During the first 4 h, ketamine and diclofenac are better than only ketamine. Diclofenac is better than CG or ketamine group at 2.6 h and 2.4 h, respectively.	Not statistically significant	Not statistically significant	—
Rahmaniam	5 min after delivery—IV 0.25 mg/kg ketamine bolus	Same scheme, but instead of ketamine IV NaCl 0.9%	If asked—100 mg rectal diclofenac suppository max every 6 h, max 4 times in 24 h. If NPS ≥5—intramuscular 50 mg petidine, max 2 times in 24 h.	CG VAS bigger that RG at 1, 2, 6, 12 h ($p < 0.001$). RG time until first analgesic longer than in the CG ($p < 0.001$). Total dose of petidine and diclofenac lower in the RG ($p < 0.001$).	Not examined	Vomiting is more common in CG ($p = 0.020$). Hallucinations are more common in the RG ($p = 0.032$).	+
Infusion during and after surgery							
Mendola	Before first incision IV 0.1 mg/kg/h ketamine infusion for 60 h	Same scheme, but instead of ketamine—IV NaCl 0.9%	If VAS > 3 p.— > PCA 5 mL max every 60 min. If not—1) IV paracetamol 45 mg/kg, 2) IV ketorolac 1.5 mg/kg, 3) morphine	Not statistically significant between NPS. 0.1 day after surgery RG needed more analgesics ($p = 0.0016$)	Not examined	Not statistically significant. RG 32, 5 vs. CG 25% experienced nausea, vomiting, hypotension, neurological symptoms.	+

Author	Research group (RG)	Control/other group (CG)	Postoperative pain management	Results			
				Pain	Overall satisfaction	Adverse reaction	Overall
Boenigk	IV 0.12 mg/kg ketamine infusion for 24 h and 0.2 mg/kg ketamine bolus during the first 30 min into Recovery Room	Same scheme, but instead of ketamine—IV NaCl 0.9% and same ketamine bolus	PCA with hydromorphone—0.2 mg max every 6 min, max 2 mg/h for 24 h in the Recovery Room. If NPS > 4—IV 0.2–0.3 mg hydromorphone.	Not statistically significant between NPS. Opioid-tolerant in RG consumed more hydromorphone than opioid-tolerant in CG (p = 0.007)	Not examined	Not statistically significant	+

Table 2.
Results of studies included in a systematic review.

consumption of opioids, the adverse reaction occurred less frequently, and overall satisfaction on pain management was better.

Different from other trials, Han with colleagues [20] did not find any statistically significant difference in reducing pain scores, overall satisfaction, and adverse reactions.

Bilgen with other researches [11] evaluated three different IV ketamine bolus doses (0.25, 0.5, 0.1 mg/kg) in patients after C-section. No differences were observed.

Menkiti with colleagues [16] found that VAS > 3 points were significantly more often assessed in the control group at 90, 120, 150 min. Also, the first analgesic was appointed for patients for a short amount of time in the research group.

Rahmaniam with colleagues [21] researched IV ketamine bolus after C-section. In the ketamine group, pain scores were lower in the 1, 2, 6, and 12 hours after surgery. Time until first analgesic and amount of them was lower in the ketamine group. Unfortunately, nausea and hallucinations occurred more frequently in the ketamine group.

Song and fellow co-authors [23] researched IV ketamine bolus (which was also given in the PCA) impacts on pain management after spinal cord surgery. At 48 hours, patients with PCA ketamine used less additional fentanyl than the control group. Also, research group participants experienced nausea at 0–6 hours and felt dizziness for 48 hours.

Honarmand and colleagues [15] discovered that 0.5 mg/kg IV ketamine bolus before appendectomy alleviates pain at 12, 18, and 24 hours better than the same dose given s/c or placebo.

Adam with other researchers [17] researched ketamine and diclofenac effects after laparoscopic cholecystectomy. It showed that ketamine without diclofenac has no significant difference.

Mendola and co-authors [12] were determined to find IV ketamine infusion, continued for 60 hours after surgery, impact on pain management. For 48 hours, the control group required more analgesics than the research group. Adverse reactions were not more common in the ketamine group.

Boenigk and colleagues [25] researched 0.2 mg/kg IV ketamine bolus and 0.12 mg/kg ketamine infusion on patients with and without opioid addiction. Those in the control group who have an addiction used more opioids for postoperative pain management than those who did not have an addiction.

4. Discussion

Multimodal analgesia is a key component for adequate and fulfilling postoperative pain management. Ketamine, together with adjuncts such as magnesium, lidocaine, dexamethasone, α2 agonists, incisional infiltration, acetaminophen, nonsteroidal anti-inflammatory drugs, or COX-2 selective given during surgery, is known to lessen the pain postoperatively by preventing neural sensitization that may lead to persistent pain as their primary purpose is to target the pain during various pathways in the central nervous system. Ketamine prescribed intravenously after the surgery may decrease overall opioid use, and it is a good analgesic for patients who develop tolerance to the analgesic properties of opioids [27].

The results of all these researches can be explained in several ways. Firstly, according to the type of surgery, Subramaniam [9] and Kim [19] investigated patients after spinal cord surgery, but Subramaniam [17] used IV ketamine 0.15 mg/kg and Kim [19] used a much bigger dose—0.5 mg/kg IV ketamine bolus. Ketamine was infused at the same speed at 24 and 48 hours, respectively. These

reasons may have contributed to better outcomes of the Kim [19] trial, as patients used less postoperative analgesics when compared to the control group. Differently from these trials, Chumbley [24] and Yazigi [18] trial results cannot be explained like that, because IV ketamine bolus dose is the same, but Chumbley [24] used 0.1 mg/kg/h infusion for 48 hours (more common adverse reactions—vivid dreams, poor well-being) and Yazigi [18] used 0.5 mg/kg/h for 78 hours, but the results were favorable to Chumbley [24] where patients needed less additional analgesics. As in Chumbley [24], trial patients felt adverse reactions more frequently the prospects of early rehabilitation of these people would have been weaker.

As for ketamine bolus and infusion only during surgery, we can state that carrying out open renal surgery [10] and cholecystectomy [22], IV ketamine bolus (0.15 mg/kg and 0.2 mg/kg), and infusion (2 μg/kg/min and 2 μg/kg/min) alleviates pain better in the first 12 and 6 hours accordingly, reducing the postoperative amount of analgesics and not causing adverse reactions. Nielsen [14] trial (0.5 mg/kg ketamine bolus and 0.25 mg/kg infusion) showed that patients who used opioids before surgery consume less morphine. Haliloglu [23] and Han's [20] trials compared IV ketamine bolus 0.5 mg/kg and infusion 0.25 mg/kg—in the first one morphine consumption was lower in the research group for 24 hours, in the second one, no difference was observed. Best results were written in the Ates [26] trial (0.5 IV ketamine bolus and 0.25 mg/kg/h infusion)—pain scores, the demand of postoperative analgesics, and adverse reactions were lower in the ketamine group. Satisfaction of pain management was better in the ketamine group in only this trial.

Three trials compare the ketamine bolus effect on postoperative pain after C-section. In the first one [11], 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg ketamine boluses did not have any impact on any factor. In the second one [16], 0.15 mg/kg ketamine bolus was determined to shorten the time of additional analgesia. In the third one [21], 0.25 mg/kg ketamine bolus revealed the best results—lower pain scores, longer time without analgesics and its dose, but nausea and hallucinations appeared more frequently. During spinal cord surgery [13], 0.3 mg/kg IV ketamine bolus triggered nausea and dizziness but lowered the number of additional analgesics. What is interesting, 0.5 mg/kg IV ketamine bolus caused fewer adverse reactions after appendectomy but also alleviated pain effectively in the first 24 hours after surgery [15]. A dose of 0.15 mg/kg IV ketamine bolus during laparoscopic cholecystectomy did not show any better results than a placebo. In only one trial, researchers investigated overall satisfaction which did not differ between the ketamine and placebo groups [17].

Comparing trials that investigated only ketamine infusion efficiency, we can summarize them into few fields—pain scores were not lower neither 0.1 mg/kg/h nor 0.12 mg/kg/h IV ketamine infusion. In the first research [12], the ketamine group required fewer postoperative analgesics. The same results were shown in the second trial, where patients before surgery used opioids [25]. Adverse reactions did not differ in any trial.

5. Conclusions

1. Pain intensity evaluated while using ketamine:

   a. Bolus and infusion (during and after surgery)—IV combination of 0.5 mg/kg ketamine bolus and 1 μg/kg/min infusion successfully lowered the necessity of postoperative analgesics,

   b. Bolus and infusion (during surgery)—IV combination of 0.5 mg/kg ketamine bolus and 0.25 mg/kg/h infusion successfully reduced postoperative pain and

IV 0.2–0.5 mg/kg bolus and 0.1–0.25 mg/kg/h infusion meaningfully diminished consumption of postoperative analgesics,

c. Infusion (during and after surgery)—IV 0.1 mg/kg/h ketamine bolus reduced consumption of postoperative analgesics,

d. Bolus—less analgesics were used when IV bolus dose were 0.25–0.3 mg/kg and IV 0.5 mg/kg bolus eased pain better for the first 24 h, 0.25 mg/kg for 12 h, 0.15 mg/kg for 3 hours.

2. In 17 trials, overall well-being and satisfaction of pain management did not differ between ketamine and placebo and in one trial, 0.5 mg/kg ketamine bolus and 0.25 mg/kg/h infusion were associated with better results.

3. Adverse reactions were more common in three pieces of research—the first being IV 0.1 mg/kg ketamine bolus and 0.1 mg/kg/infusion; second—IV 0.25 mg/kg ketamine bolus; and third—IV 0.3 mg/kg ketamine bolus, thus meaning that the early rehabilitation of patients in the rest of the trials would have been good.

6. Practical recommendations

These recommendations are prepared in accordance with guidelines issued in 2018 [6]:

1. Subanesthetic ketamine infusions should be considered for patients undergoing painful surgery (upper and lower abdominal, thoracic, and orthopedic (limbs and spine)).

2. Ketamine should be considered for both opioid-tolerant and opioid-dependent patient groups.

3. Ketamine bolus should not exceed 0.35 mg/kg, infusion 1 mg/kg/g dose, but it should always be considered according to a patient's factors.

4. Patients with cardiovascular disease, pregnant women, patients with active psychosis, hepatic dysfunction, elevated intracranial, and intraocular pressure should avoid using ketamine.

5. Intranasal ketamine should be considered using for children during short-time procedures and for whom intravenous ketamine is difficult to inject. Intranasal ketamine is effective for acute pain management and for amnesia and sedation during the procedure.

6. Evidence for the benefit of IV-PCA: Delivered ketamine as the only analgesic for acute pain is limited and there is moderate evidence for the benefit of the addition of ketamine to an opioid-based IV-PCA for acute and perioperative pain management.

Conflict of interest

The authors declare no conflict of interest.

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