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Original Research Article

The Use of Intravenous Infusion or Single Dose of Low-Dose Ketamine for Postoperative Analgesia: A Review of the Current Literature

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Abstract

Objective. As an analgesic and *N*-methyl-D-aspartate receptor antagonist, ketamine has been increasingly used as an adjunct in the management of acute perioperative pain. Although several meta-analyses have examined low-dose intravenous (IV) ketamine, they do not distinguish between different types of infusions. Additionally, the many clinical trials published on ketamine vary by regimen of administration and surgical site. This review seeks to exclusively examine the evidence supporting the use of low-dose IV infusion of ketamine for the management of perioperative pain.

Methods. We searched Medline for any clinical trials or meta-analyses that were conducted on low-dose IV infusion of ketamine between 1966 and November 2013. Using six equations, we were left with 695 references. Of those, five meta-analyses and 39 clinical trials met the criteria to be included our review. These clinical trials represent 2,482 patients, 1,403 of whom received ketamine. We then examined the efficacy of low-dose IV ketamine by regimen and site of surgery using pain scores and opioid consumption as endpoints. Finally, we assessed the safety and long-term impact of low-dose ketamine.

Results. Low-dose IV ketamine reduces opioid consumption by 40%. It also lowers pain scores, but these findings are less clear. No major complications have been reported with low-dose IV infusion of ketamine when given up to 48 hours after surgery. While our review lends support to using low-dose IV infusion of ketamine in the management of perioperative pain, its optimal dose and regimen remain to be determined.

Conclusions. Thirty-nine clinical trials assessed a continuous infusion or a bolus of low-dose ketamine for postoperative analgesia using reduction of pain scores or reduction of the opioid consumption as the primary endpoint. The mean reduction of opioid consumption when using low-dose IV infusion ketamine (infusion rate less than 1.2 mg/kg/h) is 40%. Ketamine also reduces pain scores, but the amplitude of the effect is less clear. No major complications have been reported with low-dose IV infusion of ketamine up to 48 hours following surgery.

Key Words. Low-Dose; Ketamine; Postoperative Analgesia; Intravenous; Infusion; Review

Introduction

A multimodal approach to analgesia is now recommended for managing acute pain. By using different analgesics

to simultaneously target distinct pain mechanisms, multimodal analgesia has been reported to improve analgesia and reduce opioid consumption [1].

Ketamine, an anesthetic first developed in 1970 [2], is one drug that has gained renewed interest as part of the multimodal approach toward acute pain treatment [3]. As an *N*-methyl-D-aspartate (NMDA) receptor antagonist [4,5], ketamine can function as an analgesic by blocking the NMDA receptors involved in nociceptive and inflammatory pain transmission [6]. Knowledge of ketamine's analgesic properties and mechanism of action has led to the development of clinical trials to assess the drug's ability to mitigate various pain syndromes, including cancer [7], neuropathic [8], refractory chronic [9], and acute pain [10]. Ketamine's association with untoward side effects [11], however, has deterred some from administering the drug in the perioperative setting.

Currently, the method by which ketamine is administered in the context of acute pain management varies considerably. Indeed, ketamine has been administered through different routes including oral, intravenous (IV), epidural, and wound infiltration. The dose of ketamine has also varied, ranging from single dose boluses (up to 1 mg/kg) to continuous IV infusions (up to 0.18 mg/kg/h for 48 hours postoperative) [12,13].

At the University of Pittsburgh Medical Center (UPMC) (Pennsylvania), Division of Regional Anesthesia and Acute Interventional Perioperative Pain, low-dose continuous IV infusion of ketamine has been included as a standard of care for the management of postoperative pain in opioid tolerant patients since June 2010.

The aim of this article is to review the evidence associated with giving low-dose IV infusion of ketamine in the perioperative period for acute pain. Accordingly, low-dose IV ketamine is defined as the administration of no more than 1.2 mg/kg/h when used as a continuous infusion and as no more than 1 mg/kg when given as a bolus [14]. Importantly, because we are performing a comprehensive review exclusively on low-dose IV infusion of ketamine, we will be able to more effectively evaluate the safety and efficacy of ketamine for this class of regimens compared with previous reviews that did not distinguish between this and other means of ketamine administration.

Methods

Literature Review

A Medline (PubMed) search was conducted for any clinical trials or meta-analyses related to low-dose IV ketamine continuous infusions and single bolus doses administered during the perioperative period between 1966 and November 2013. Using several research equations, 695 references were identified. Next, specific inclusion and exclusion criteria were applied (Figure 1) to identify the articles specifically related to the administration of low-dose ketamine infusions. Accordingly, this review was based on 39 clinical trials, and five meta-analyses were included in our review. To confirm a systematic research and that no references were missing, the meta-analyses' bibliographies were cross-reviewed. Articles were reviewed by at least two different reviewers who compared their findings.

Out of the 39 clinical trials on low-dose IV infusion ketamine, 26 were conducted on continuous infusions following a bolus dose, 11 on single bolus doses, and two on continuous infusions only. We reviewed each reference to evaluate ketamine's analgesic effect by measuring changes in patient opioid consumption and pain scores. Additionally, we evaluated ketamine's safety by assessing the number of adverse events and side effects associated with the drug.

The 39 clinical trials that we reviewed represent a total of 2,482 patients, 1,403 of whom received ketamine. The distribution of studies according to the type of surgery was the following: spine surgery (seven studies); cardiac surgery (one study); bowel surgery (22 studies); arthroplasty or ligament repair surgery (six studies); ear, nose, and throat surgery (one study); and a combination of surgeries (two studies). In addition, the five meta-analyses included 137 studies conducted on different routes, regimens, and aims for ketamine's administration. Out of these 137 studies, only 23 were therefore included in our review.

Typically, the two main methods used to measure the extent of analgesia in clinical trials are the reduction of pain scores and the reduction of opioid consumption. In most cases, studies specify which of these criteria was chosen as the primary endpoint to calculate statistical power. Using this distinction (i.e., pain scores or opioid consumption used as first endpoint), we sorted the 39 clinical trials studies used in our review into three groups. The first group includes 24 studies which used opioid consumption as first endpoint. The second group gathers 10 studies using pain scores as first endpoint. Finally, the third group concerns studies which did not report a primary endpoint or used endpoints aside from pain scores or opioid consumption (one was only descriptive [15], one did not report on their primary endpoint [16], three used pain scores and opioid consumption as their secondary endpoints while using as primary endpoint: time to first analgesic [17] or hyperalgesia [18,19]). For this last group, studies were included only to assess ketamine's safety, not efficacy.

Efficacy of Ketamine

The Analgesic Effect of Ketamine According to the Meta-Analyses

All of the five meta-analyses concluded that IV ketamine increases analgesia by reducing pain scores as well as opioid consumption. These meta-analyses, however, combine different routes of administration [4,12–14,20], making it difficult to disentangle the analgesic effect of IV ketamine given through continuous infusion from that

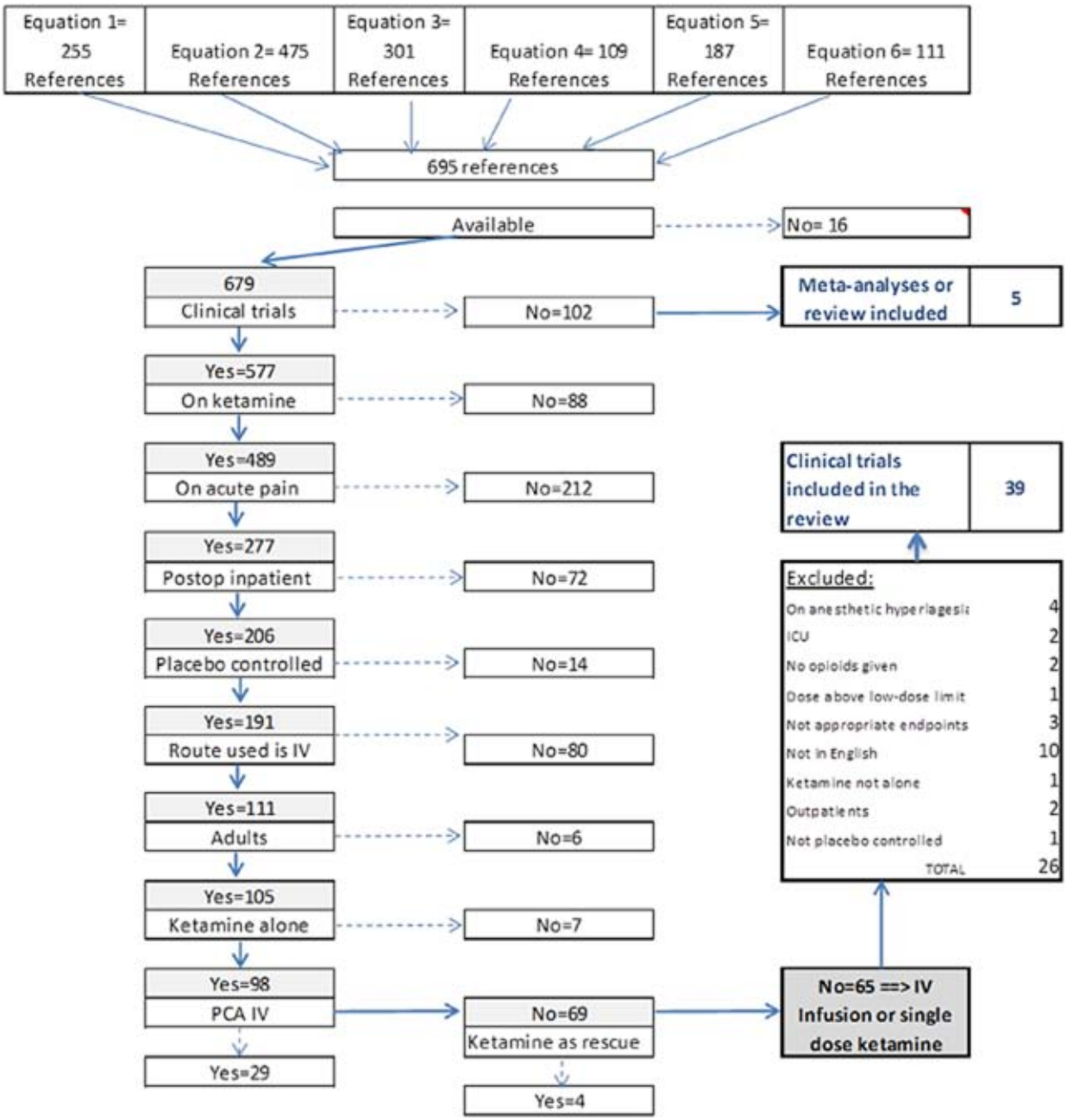

Figure 1 Inclusion and exclusion criteria of our review. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

given through patient-controlled analgesia (PCA). Hence, because we are seeking to examine only continuous IV infusions of ketamine (or bolus doses), findings from these meta-analyses have significant limitations.

All of the meta-analyses agree on the opioid-sparing effect of ketamine, with the magnitude of this effect varying from one review to another. Three meta-analyses reported a median reduction of morphine consumption of 32% [12] to 50% [14] and a reduction of rescue analgesics of 30–50% [13]. Two of those three reviews also used a weighted mean difference (WMD) to assess opioid intake and found that ketamine reduced cumulative opioid consumption [12] or the total intake of rescue analgesics [13] by 16 mg. One review [4] reported a standard deviation in means for total opioid intakes of –0.631. Finally, the last review [20] reported an opioid-sparing effect with no data regarding the effect mentioned.

Similarly, all five meta-analyses found that ketamine reduces pain scores. In four of the five meta-analyses, pain scores at 24 hours postoperative were reported to be

significantly reduced with IV ketamine in 87.5% [14], 59% [20], 54.5% [13], and 25% [4] of the studies reviewed, respectively. Using a 10-cm visual analog scale (VAS) for pain, one review reported a WMD of –0.85cm for single doses and –0.82 for continuous infusions [20] and another one a WMD of 0.35cm, yielding a reduction of pain intensity of 20% [12].

Efficacy of Low-Dose IV Infusion of Ketamine Reported in Clinical Trials: According to the Regimen Used

To analyze the efficacy of low-dose IV ketamine according to the regimen used, the clinical trials first were sorted and then subdivided by the regimen used by primary endpoints (opioid consumption or pain scores) (infusion only, infusion following a bolus dose or single dose). Since in five cases no primary end points were defined, only 34 clinical trials will be detailed in this section (Tables 1–3).

Studies that Used Reduction of Opioid Consumption as Their First Endpoint

Infusion Only. Only one study [21] that assessed ketamine's efficacy with the reduction of opioid consumption as its first endpoint looked at IV ketamine given solely as an infusion postoperatively. Adriaenssens et al. [21] administered to naïve opioid patients a 0.15 mg/kg/h infusion of ketamine for 48 hours. The authors reported a 38% reduction of morphine consumption for the first 24 hours postoperative (ketamine = 19 mg vs placebo = 31 mg) and 48% for 48 hours postoperative (ketamine = 28 mg vs placebo = 54 mg). They found no associated change in pain score at 24 hours postoperative (ketamine = 2.5 vs placebo = 3.6 on a 10-mm VAS).

Infusion Following a Bolus Dose

Intraoperative Bolus and Intraoperative Infusion of Low-Dose Ketamine. Six studies [22–27] assessed the use of ketamine intra-operatively (intraoperative bolus + continuous infusion). These studies represent 456 patients, 252 of whom received ketamine. The dose ranged from 0.15 mg/kg + 0.12 mg/kg/h [22] to 0.5 mg/kg + 0.6 mg/kg/h [26].

Out of the six studies, four studies reported an opioid-sparing effect with two of them reporting also a significant reduction of pain scores for up to 12 hours post-operative. For these four studies, ketamine reduced opioid consumption by an average of 39.25% at 24 hours postoperative [22,25–27]. Kararmaz et al. [25] found a 26% reduction of morphine consumption at 24 hours postoperative (ketamine = 60.3 mg vs placebo = 81.6 mg) and a significant reduction of pain scores for 6 hours postoperative (VAS pain scores equal to ketamine = 1.5 vs placebo = 4.0 at 6 hours postoperative and to 2.0 for both groups at 24 hours postoperative on a 10-cm VAS) when administrating a bolus of 0.5 mg/kg followed by an intraoperative infusion of 0.5 mg/kg/h. Parikh et al. [27] administered a bolus dose of 0.15 mg/kg followed by an infusion of 0.12 mg/kg/h and reported a 68% reduction of morphine consumption at 24 hours postoperative (ketamine = 5.8 mg vs placebo = 18.1 mg of morphine). Pain scores were also significantly reduced for 12 hours postoperative with ketamine (VAS pain scores for ketamine = 20 vs placebo = 74 on a 100-mm VAS) and equal in both ketamine and placebo groups to 20 at 24 hours postoperative.

With a regimen of 0.15 mg/kg + 0.12 mg/kg/h, Guignard et al. [22] found a 33% reduction of morphine at 24 hours postoperative (ketamine = 46 mg vs placebo = 69 mg), while no difference was reported regarding VAS pain scores (no data given). Loftus et al. [26], who used a regimen of 0.5 mg/kg + 0.6 mg/kg/h, reported a 30% reduction of morphine at 24 hours postoperative (ketamine = 142 mg vs placebo = 202 mg) along with a reduction of 37% at 48 hours postoperative (ketamine = 195 mg vs placebo = 305 mg) and equal pain scores at 24 hours postoperative (ketamine = 4.7 vs placebo = 4.8 on a 10-cm VAS).

By contrast, two studies out of the six [23,24] reported neither a significant reduction of opioid consumption nor an improvement in pain scores with ketamine. Ganne et al. [23] who used a regimen of 0.15 mg/kg + 0.12 mg/kg/h found no significant difference between patients receiving ketamine and placebo in terms of opioid consumption (ketamine = 33.3 mg vs placebo = 31.9 mg of morphine) or VAS pain scores (ketamine = 1.4 vs placebo = 1.6 at 24 hours postoperative on a 10-cm VAS). Likewise, Katz et al. [24] used a 0.2 mg/kg + 0.15 mg/kg/h regimen and found no difference in opioid consumption (ketamine = 92.3 mg vs placebo = 103.6 mg of morphine at 72 hours postoperative) or VAS pain scores (ketamine = 1.8 vs placebo = 1.6 at 24 hours postoperative on a 10-cm VAS) between patients given ketamine or placebo.

Intraoperative Bolus and 2-Hour Postoperative Infusion of Low-Dose Ketamine. One study [28] assessed a regimen of a bolus dose of 0.5 mg/kg, followed by a 2-hour postoperative infusion of 0.12 mg/kg/h. The authors reported no significant effect of ketamine on either VAS pain scores (ketamine = 1 vs placebo = 1.4 at 24 hours postoperative on a 10-cm VAS) or morphine consumption (ketamine = 39 mg vs placebo = 29 mg of morphine at 24 hours postoperative). Notably, the authors attributed the absence of effect due to the use of a continuous intraoperative opioid analgesic.

Intraoperative Bolus and 24-Hour Postoperative Infusion of Low-Dose Ketamine. Five studies [29–32,33] assessed an intraoperative bolus and 24-hour postoperative infusion of low-dose ketamine, representing 446 patients, 255 of whom received ketamine. For this regimen, the dose ranged from a bolus of 0.15 mg/kg with a continuous infusion of 0.12 mg/kg/h [29] to a bolus of 1 mg/kg with a continuous infusion of 0.083 mg/kg/h [32].

Table 1 Studies included for efficacy and safety with opioid consumption as first endpoint

Name of Study	Dose Used	Regimen	Ketamine Patients	Placebo Patients	First Endpoint	OSE/Reduction at 24 Hours If Not Specified	Pain (Time of Significant Difference)
Postoperative-only regimen							
Adriaenssens et al. [21]	0.15 mg/kg/h	Postop only	15	15	Opioid consumption	38%	0
Intraoperative regimen							
Guignard et al. [22]	0.15 mg/kg + 0.12mg/kg/h until skin closure	Intraop	25	25	Opioid consumption	33%	0
Ganne et al. [23]	0.15 mg/kg + 0.12 mg/kg/h	Intraop	30	31	Opioid consumption	0	0
Katz et al. [24]	0.2 mg/kg + 0.15 mg/kg/h	Intraop	97	46	Opioid consumption	0	0
Kararmaz et al. [25]	0.5 mg/kg + 0.5 mg/kg/h	Intraop	20	20	Opioid consumption	26%	6 hours postop
Loftus et al. [26]	0.5 mg/kg + 0.6 mg/kg/h	Intraop	50	52	Opioid consumption	30%	0
Parikh et al. [27]	0.15 mg/kg + 0.12 mg/kg/h	Intraop	30	30	Opioid consumption	68%	12 hours postop
Intraoperative + 2-hour postoperative regimen							
Jaksch et al. [28]	0.5 mg/kg + 0,12 mg/kg/h	Intraop + 2 hours postop	15	15	Opioid consumption	0	0
Intraoperative + 24-hour postoperative regimen							
Subramaniam et al. [29]	0.15 mg/kg + 0.12 mg/kg/h	Intraop + 24 hours postop	15	15	Opioid consumption	0	0
Urban et al. [30]	0.2 mg/kg + 0.002 mg/kg/h	Intraop + 24 hours postop	12	12	Opioid consumption	0	24 hours postop
Remerand et al. [31]	0.5 mg/kg + 0.12 mg/kg/h	Intraop + 24 hours postop	75	79	Opioid consumption	28%	0
Yamauchi et al. [32] Cervical	1 mg/kg + 0.042 mg/kg/h (= 1 mg/kg/24 hours)	Intraop + 24 hours postop	22	23	Opioid consumption	18% (up to 12 hours)	0
Yamauchi et al. [32] Lumbar	1 mg/kg + 0.042 mg/kg/h (= 1 mg/kg/24 hours)	Intraop + 24 hours postop	23		Opioid consumption	0	0
Yamauchi et al. [32] Cervical	1 mg/kg + 0.083 mg/kg/h (= 2 mg/kg/24 hours)	Intraop + 24 hours postop	42	44	Opioid consumption	18.75%	24 hours postop
Yamauchi et al. [32] Lumbar	1 mg/kg + 0.083 mg/kg/h (= 2 mg/kg/24 hours)	Intraop + 24 hours postop	46		Opioid consumption	0	0
Stessel et al. [33]	0.2 mg/kg + 0.12 mg/kg/h	Intraop + 24 hours postop	17	18	Opioid consumption (study stopped)	0	0
Intraoperative + 48-hour postoperative regimen							
Kim et al. [34]	0.5 mg/kg bolus + 0.06 mg/kg/h	Intraop + 48 hours postop	18	17	Opioid consumption	0	0
Kim et al. [34]	0.5 mg/kg bolus + 0.12 mg/kg/h	Intraop + 48 hours postop	17		Opioid consumption	42.6% at 48 hours postop	0
Zakine et al. [35]	0.5 mg/kg Bolus + 0.12 mg/kg/h	Intraop + 48 hours postop	50	27	Opioid consumption	46% at 48 hours postop	48 hours postop
Adam et al. [36]	0.5 mg/kg + 0.18 mg/kg/h + 0.09 mg/kg/h	Intraop + 48 hours postop	20	20	Opioid consumption	34.7% at 48 hours postop	0
Lahtinen et al. [37]	0.075 mg/kg + 0.075 mg/kg/h	Intraop + 48 hours postop	44	46	Opioid consumption	17% at 48 hours postop	0
Aveline et al. [38]	0.2 mg/kg + 0.12 mg/kg/h intraop + 0.06 mg/kg/h for 48 hours postop	Intraop + 48 hours postop	25	24	Opioid consumption	29.9% at 48 hours	48 hours postop
Single dose regimen							
Kafali et al. [39]	0.15 mg/kg	Single dose	30	30	Opioid consumption	18%	30 minutes postop
Kwok et al. [40]	0.15 mg/kg	Single dose	90	45	Opioid consumption	56%	6 hours postop
Dullenkopf et al. [41]	0.15 mg/kg	Single dose	36	33	Opioid consumption	0	0
Menigaux et al. [42]	0.15 mg/kg	Single dose	30	15	Opioid consumption	52.5%	0
Dullenkopf et al. [41]	0.5 mg/kg	Single dose	41		Opioid consumption	0	0
Aveline et al. [43]	0.15 mg/kg	Single dose	23	23	Opioid consumption	57%	up to 48 hours postop
Argiriadou et al. [44]	0.5 mg/kg + 0.2 mg/kg/20 minutes	Single dose (repeated)	15	15	Opioid consumption: Additional analgesic	Reduction but unknown data	6 hours postop
Argiriadou et al. [44]	0.5 mg/kg	Single dose	15		Opioid consumption: Additional analgesic	0	0

Table 2 Studies included for efficacy and safety with "pain scores" as first endpoint

Name of Study	Dose Used	Regimen	Ketamine Patients	Placebo Patients	First Endpoint	OSE/Reduction at 24 Hours If Not Specified	Pain (Time of Significant Difference)
Postoperative-only regimen							
Barreveld et al. [45]	0.2 mg/kg/h	Postop only	29	30	Pain: Numeric Rating Scale pain scores	0	Average pain up to 24 hours postop
Intraoperative regimen							
Sen et al. [46]	0.3 mg/kg + 0.05 mg/kg/h	Intraop	20	20	Reduction of pain	42%	0
Aida et al. [47]	1 mg/kg + 0.5 mg/kg/h	Intraop	29	31	Pain	20%	24 hours postop
Intraoperative + 24-hour postoperative regimen							
Edwards et al. [48]	1 mg/h morphine + 5, 10, 20 mg/kg of ketamine up to 24 hours postop	Intraop + 24 hours postop	30	10	Pain	0	0
Intraoperative + 48-hour postoperative regimen							
Ilkjaer et al [49]	10 mg + 10 mg/h	Intraop + 48 hours postop	24	28	VAS pain scores	0	0
Webb et al. [50]	0.3 mg/kg + 0.1 mg/kg/h	Intraop + 48 hours postop	56	64	Pain: Improvement of subjective analgesic efficacy	45% at 48 hours postop	AUC lower
Single dose regimen							
Safavi et al. [51]	1 mg/kg	Single dose	30	30	VAS pain scores	84,6%	24 hours postop
Roytblat et al. [52]	0.15 mg/kg	Single dose	11	11	Pain	39,4%	4 hours postop
Behdad et al. [53]	0.5 mg/kg	Single dose	40	40	Pain	70%	24 hours postop
Dahl et al. [54]	0.4 mg/kg	Single dose	60	29	Pain	0	6 hours postop

Table 3 Studies included only for safety

Name of Study	Dose Used	Regimen	Ketamine Patients	Placebo Patients	First Endpoint	OSE/Reduction at 24 Hours If Not Specified	Pain (Time of Significant Difference)
Xie et al. [16]	0.5 mg/kg	Single dose	28	14	Not reported	30%	24 hours postop
Hadi et al. [17]	0.06 mg/kg/h	Intraop	15	15	Time to first request of analgesic	24,5%	24 hours postop
Hadi et al. [17]	0.06 mg/kg/h	Intraop + 24 hours postop	15		Time to first request of analgesic	55%	24 hours postop
Perrin and Purcell [15]	0.5 mg/kg + 0.24 mg/kg/h	Intraop	5	7	Only descriptive	18% (for 48 hours)	0
De Kock et al. [19]	0.25 mg/kg + 0.125 mg/kg/h	Intraop	20	20	Pain: hyperalgesia	0	0
De Kock et al. [19]	0.5 mg/kg + 0.25 mg/kg/h	Intraop	20		Pain: hyperalgesia	Reduction but no data	0
Stubhaug et al. [18]	0.5 mg/kg + 0.12 mg/kg/h for 24 hours + 0.06 mg/kg/h for 48 hours	Intraop + 48 hours postop	10	10	Postop hyperalgesia	0	0

Out of the five studies, only Yamauchi et al. [32] reported a reduction of opioid consumption with a concomitant decrease in pain scores. While administering a regimen of 1 mg/kg + 0.083 mg/kg/h of ketamine—the highest infusion rate in their study—they reported a reduction of 18.75% of fentanyl consumption at 24 hours postoperative (ketamine = 13 mcg/kg vs placebo = 16 mcg/kg) along with a 16.67% reduction at 48 hours postoperative (ketamine = 25 mcg/kg vs placebo = 30 mcg/kg) and a reduction of pain scores up to 48 hours postoperative (VAS pain scores: ketamine = 1 vs placebo = 18 on a 100-mm VAS). It is important to note that this regimen was shown to be efficacious for patients that underwent cervical, but not lumbar, surgery.

Out of these five studies, two [31,32] reported a reduction of opioid consumption with no accompanying decrease in pain scores. Using their lowest rate of 1 mg/kg + 0.042 mg/kg/h, Yamauchi et al. [32] reported an 18% reduction of fentanyl consumption up to 12 hours postoperative (ketamine = 7 mcg/kg vs placebo = 8.5 mcg/kg; at 24 hours postoperative, fentanyl consumption was equal to 15 mcg/kg for the ketamine group and to 16 mcg/kg for the placebo group) but equal VAS pain scores for both groups at 24 hours postoperative (around 20 for both groups on a 100-mm VAS). Similarly, using a regimen of 0.5 mg/kg + 0.12 mg/kg/h, Remerand et al. [31] reported a 28% reduction of morphine consumption up to 24 hours postoperative (ketamine = 14 mg vs placebo = 19 mg) without a difference in Numeric Rating Scale (NRS) pain scores between the two groups at this time point (ketamine = 14 vs placebo = 15 on a 100-mm NRS).

For those two studies [31,32], ketamine lowered opioid consumption at 24 hours postoperative by an average of 23.375%.

Of the five studies employing an intraoperative bolus and 24-hour postoperative infusion of low-dose ketamine, one [30] reported a significant reduction of pain scores with no accompanying change in opioid intake. In administering a regimen of 0.2 mg/kg + 0.002 mg/kg/h, Urban et al. [30] found that at 24-hour postoperative ketamine significantly reduced NRS pain scores (ketamine = 3.6 vs placebo = 5.5 on a 10-cm NRS) without having a significant effect on morphine consumption (ketamine = 18.5 mg vs placebo = 27 mg). Although the results for the opioid consumption did not reach significance, they indicate that ketamine decreased opioid intake study by 31%.

Finally, the last two studies [29,33] of this group detected neither a reduction of opioid consumption nor a reduction of pain scores. In their paper, Subramaniam et al. [29] used a regimen of 0.15 mg/kg bolus + 0.12 mg/kg/h and reported no significant differences between ketamine and placebo in morphine consumption (ketamine = 40.42 mg vs placebo = 38.24 mg) or VAS pain scores at 48 hours postoperative (ketamine = 4.3 vs placebo = 4.8 on a 10 cm VAS). Similarly, in administering a bolus of 0.2 mg/kg followed by an infusion of 0.12 mg/kg/h for 24

hours postoperative, Stessel et al. [33] reported no significant reduction of piritramide consumption (ketamine = 21 mg vs placebo = 26 mg at 24 hours postoperative) or VAS pain scores (ketamine = 14 vs placebo = 23 on a 100-mm VAS, with a difference of area under the curve of $P = 0.21$). It is noteworthy, however, that Stessel et al. [33] had to stop the clinical trial early, leaving their study underpowered because too few patients were enrolled. The authors suggest this might be the reason why their findings were not significant.

Taken together, these five studies suggest that low-dose ketamine—when given as an intraoperative bolus and 24-hour postoperative infusion—is effective in reducing opioid consumption when the bolus dose is greater than or equal to 0.5 mg/kg. Regarding pain scores, it appears that the specific analgesic protocol may play a critical role in ketamine's ability to significantly alter this outcome. Indeed, from the four studies that were completed, those that reported a significant difference in pain scores only used PCA containing morphine or fentanyl [30,32], while those that found no significant difference used a multimodal approach to analgesia [29,31]. Specifically, those that used multimodal analgesia used either an epidural bupivacaine infusion [29] or a combination of ketoprofen and paracetamol [31].

Intraoperative Bolus and 48-Hour Postoperative Infusion of Low-Dose Ketamine. There are five clinical trials [34,35–38] that assessed an intraoperative bolus of ketamine followed by a continuous infusion of ketamine for 48 hours postoperative that used reduction of opioid consumption as their first endpoint. In total, these trials represent 308 patients, 174 of whom received ketamine. In these five studies, the dose ranged from a bolus of 0.075 mg/kg followed by an infusion of 0.075 mg/kg/h [37] to a bolus of 0.5 mg/kg followed by an infusion of 0.18 mg/kg/h (first 24 hours postoperative) + 0.09 mg/kg/h (from 24 hours to 4 hours postoperative) [36].

All five studies using this regimen found that ketamine had an opioid-sparing effect [34,35–38], though not all were associated with a concomitant decrease in pain scores. With this regimen, the mean reduction in opioid consumption across studies was 34.16%. At only the lowest infusion rate in one of these studies did ketamine have no impact on either opioid intake or pain scores [34].

Out of these five studies, two [35,38] reported a significant reduction of both opioid consumption and pain scores. Zakine et al. [35] conducted a study on a regimen of 0.5 mg/kg bolus followed by an infusion of 0.12 mg/kg/h of ketamine. They observed a 46% reduction of morphine consumption (ketamine = 27 mg vs placebo = 50 mg) and reduced VAS pain scores up to 48 hours postoperative (ketamine: 0 vs placebo = 25 on a 100-mm VAS). Aveline et al. [38] administrated a bolus dose of 0.2 mg/kg followed by an intraoperative infusion of 0.12 mg/kg/h and a postoperative infusion of 0.06 mg/kg/h for 48 hours. At 48 hours postoperative, they reported a 29.9% decrease in morphine consumption (ketamine = 50.5 mg vs placebo = 72.1 mg) as well as significantly lower VAS pain scores (ketamine = 23 vs placebo = 33 on a 100-mm VAS, $P < 0.001$).

Three of these five studies assessing an intraoperative bolus followed by an infusion of ketamine for 48 hours postoperative [34,36,37] reported a reduction of opioid consumption with no change in pain scores. Using their highest regimen of 0.5 mg/kg/h + 0.12 mg/kg/h, Kim et al. [34] found a 42.6% reduction of fentanyl consumption (ketamine = 474 mcg vs placebo = 826 mcg) but no change in VAS pain scores (ketamine = 29 vs placebo = 34 on a 100-mm VAS) for 48 hours postoperative. Similarly, with a ketamine regimen of 0.075 mg/kg + 0.075 mg/kg/h, Lahtinen et al. [37] reported a 17.6% reduction of morphine intake at 48 hours postoperative (ketamine = 103 mg vs placebo = 125 mg) with no accompanying change in VAS pain scores (ketamine = 2.2 vs placebo = 2.9 on a 10 cm VAS) at 32 hours postoperative. Finally, in administering a regimen of 0.5 mg/kg + 0.18 mg/kg/h for 24 hours postoperative and 0.09 mg/kg/h until 48 hours postoperative, Adam et al. [36] reported a 34.7% reduction of morphine intake (ketamine = 45 mg vs placebo = 69 mg) but equal VAS pain scores (ketamine = 15 vs placebo = 22 on a 100-mm VAS) at 48 hours postoperative.

Only at their lowest infusion rate did Kim et al. [34] find that ketamine decreased neither fentanyl consumption (ketamine = 756 mcg vs placebo = 826 mcg) nor pain scores (ketamine = 29 vs placebo = 34 on a 100-mm VAS). This regimen consisted of a bolus dose of 0.5 mg/kg followed by an infusion of 0.06 mg/kg/h.

Bolus Dose Only. Six studies [39–44] assessed the efficacy of a bolus dose of ketamine, representing a total of 441 patients, 280 of whom received ketamine. The doses assessed ranged from 0.15 mg/kg to 0.5 mg/kg. One study [44] assessed two regimens (one using a single dose of 0.5 mg/kg and one using repeated boluses of 0.2 mg/kg during the surgery).

Out of the six studies, one [43] reported a reduction of both opioid consumption and pain scores. In this study, the authors compared the combination of ketamine and morphine (0.15 mg/kg bolus of ketamine + 0.1 mg/kg of morphine) to morphine alone (0.1 mg/kg). With the combination of ketamine and morphine, Aveline et al. [43] reported a 57% reduction of morphine consumption at 24 hours postoperative (ketamine + morphine = 15 mg vs morphine alone = 35 mg) as well as reduced VAS pain scores up to 48 hours postoperative (ketamine + morphine = 28 vs morphine alone = 35 on a 100-mm VAS).

Four of these same six studies [39,40,42,44] found a reduction of opioid consumption with no accompanying decrease in VAS pain scores at 24 hours postoperative. Using a bolus dose of 0.15 mg/kg, Kafali et al. [39] reported an 18% decrease in morphine intake at 24 hours postoperative (ketamine = 44.2 mg vs placebo = 53.9 mg) with a change in VAS pain scores that was only

significant at 30 minutes postoperative (ketamine = 3.00 vs placebo = 2.06 on a 10-cm VAS) but not 24 hours postoperative (ketamine = 1.13 vs placebo = 1.71). Using the same bolus dose of 0.15 mg/kg, Kwok et al. [40] reported a 56% reduction of morphine consumption at 24 hours postoperative (ketamine = 1.5 mg [preincision] vs placebo = 3.4 mg) with a decrease in VAS pain scores that was significant at 6 hours postoperative (ketamine = 11 vs placebo = 20 on a 100-mm VAS) but not at 24 hours postoperative (ketamine = 9 and placebo = 14). Also, using also a bolus dose of 0.15 mg/kg, at 24 hours postoperative, Menigaux et al. [42] reported a 52.5% reduction of morphine consumption (ketamine = 34.3 [preincision] and 29.5 mg [postincision] vs placebo = 67.7 mg) with no significant difference in VAS pain scores (ketamine = 2.2 vs placebo = 4.2 on a 10-cm VAS), despite observing a 2-point difference of pain scores between the ketamine and placebo groups. Finally, when administering repeated boluses of 0.2 mg/kg ketamine throughout surgery following a preincisional bolus of 0.5 mg/kg, Argiriadou et al. [44] reported decreased intake of diclofenac and dextropropoxyphene (data on actual consumption are difficult to interpret from the clinical trial results), with reduced VAS pain scores at 6 hours postoperative (ketamine = 2 vs placebo = 3 on a 10-cm VAS) but equal at 24 hours postoperative (ketamine = 3 and placebo = 4).

For these studies, ketamine lowered opioid consumption after 24 hours postoperative by an average of 45.88%.

By contrast, two studies out of the six using bolus doses of ketamine [41,44] reported neither an opioid-sparing effect nor a reduction of pain scores. Dullenkopf et al. [41] assessed two different bolus doses of 0.15 mg/kg and 0.5 mg/kg and reported no difference in morphine consumption for either dose at 24 hours postoperative (ketamine = 8.5 mg and 9.0 mg for 0.15 mg/kg and 0.5 mg/kg doses, respectively, vs placebo = 10.3 mg). No data were given concerning pain scores at 24 hours postoperative. In contrast to the first regimen described above, Argiriadou et al. [44] found that their single bolus dose of 0.5 mg/kg had no effect on either opioid consumption or pain scores at 24 hours postoperative (equal to 4 for both groups).

Studies that Used Reduction of Pain as Their First Endpoint

Infusion Only. Only one study [45] that administered a postoperative IV infusion of ketamine alone used reduction of pain scores as its first endpoint. In this study, Barreveld et al. [45] gave an infusion of 0.2 mg/kg/h for 19.5 hours postoperative to chronic pain patients. They found that patients who were treated with ketamine reported average NRS pain scores (percent change between postoperative and preoperative NRS) 1.3 points lower than those in the placebo group at 24 hours postoperative (ketamine = 6.0 vs placebo = 7.3). There was no difference, however, in the "worst" (ketamine = 8.7 vs placebo = 9.0) or "least" (ketamine = 4.4 vs placebo = 5.6) pain scores. The authors also found no significant difference in opioid consumption at 24 hours postoperative (ketamine = 726 mg vs placebo = 770 mg).

Infusion Following a Bolus

Intraoperative Bolus and Infusion of Low-Dose Ketamine. Two studies [46,47] assessed an intraoperative regimen of ketamine with reduction of pain as the primary endpoint, representing 100 patients, 49 of whom received ketamine. Both studies reported a reduction of opioid consumption, while only one observed a concomitant improvement in pain scores. Specifically, Aida et al. [47] used a regimen 1 mg/kg + 0.5 mg/kg/h and found a 20% reduction of morphine (ketamine = 6 mg vs placebo = 7.5 mg) and an improvement of VAS pain scores (ketamine = 20 vs placebo = 27 on a 100-mm VAS) at 24 hours postoperative. By contrast, Sen et al. [46] administered a bolus dose of 0.3 mg/kg followed by an intraoperative infusion of 0.05 mg/kg/h and reported a 42% reduction of morphine consumption (ketamine = 28 mg vs placebo = 48 mg) without a difference in VAS pain scores (ketamine = 1.0 vs placebo = 1.0 on an 11-point VAS) at 24 hours postoperative.

Intraoperative Bolus and 24-Hour Postoperative Infusion of Low-Dose Ketamine. Edwards et al. [48] assessed an intraoperative bolus followed by a 24-hour postoperative infusion of ketamine using pain as its first endpoint. The authors conducted their study on four different groups: morphine alone (G1: 1 mg/h) and combinations of morphine (1 mg/h) and ketamine using different doses of ketamine (G2: 5 mg/h, G3: 10 mg/h, G4: 20 mg/h). They reported a reduction of neither opioid consumption (G1 = 47.7 mg, G2 = 35.1 mg, G3 = 43.2 mg, G4 = 36.3 mg of morphine) nor pain scores (pain scores given in pain scale of none, mild, moderate, severe, and very severe) at 24 hours postoperative.

Intraoperative and 48-Hour Postoperative Infusion of Low-Dose Ketamine. Two studies [49,50] assessed an intraoperative bolus followed by a 48-hour postoperative infusion of ketamine with pain as their first endpoint. Ilkjaer et al. [49] used reduction of VAS pain scores while Webb et al. [50] used improvement of subjective analgesic efficacy. Those two studies represent 172 patients, 80 of whom received ketamine.

Webb et al. [50] administered a bolus dose of 0.3 mg/kg followed by an infusion of 0.1 mg/kg/h for 48 hours postoperative. They reported a 45% reduction of morphine consumption (ketamine = 35 mg vs placebo = 63.5 mg) and lower VRS pain scores ($P = 0.01$ at rest and $P = 0.02$ with movement) at 48 hours postoperative. Ilkjaer et al. [49], on the other hand, found the opposite assessing a bolus dose of 10 mg (equal to 0.13 mg/kg with a median weight of 75 kg for both groups) followed by an infusion of 10 mg/h (0.13 mg/kg/h) for 48 hours postoperative. They reported no reduction of morphine consumption (with no difference in the mean number of morphine doses patients in either the ketamine or placebo received; ketamine = 9

vs placebo = 12) and no reduction of pain scores (equal to 0 for both groups at rest at 24 hours postoperative; ketamine = 9 vs placebo = 8 at 4 hours postoperative on a 100-mm VAS). This lack of significance, however, should be interpreted with caution as the pain scores for both groups are very low.

Bolus Dose Only. Four studies [51–54] assessed a single dose of low-dose ketamine using a reduction of pain as their first endpoint. This represents 251 patients, 141 of whom received ketamine.

Out of the four studies, two [51,53] reported a reduction of opioid consumption along with a reduction of pain scores for 24 hours postoperative. Safavi et al. [51] administered a bolus dose of 1 mg/kg and reported an 84.6% decrease in mepiridine consumption (ketamine = 23.3 mg vs placebo = 151.0 mg at 24 hours postoperative), the greatest reduction of opioid consumption out of any study included in our review. These authors also observed decreased VAS pain scores at 24 hours postoperative (ketamine = 0.1 vs placebo = 5.8 on a 10-cm VAS). Giving a single dose of 0.5 mg/kg, Behdad et al. [53] reported a 70% reduction of pethidine consumption at 24 hours postoperative (ketamine = 0.6 mg vs placebo = 2.0 mg) and reduced VAS pain scores (ketamine = 1.3 vs placebo = 1.8 at 24 hours postoperative and ketamine = 4.5 vs placebo = 6.6 at the first time of complete consciousness on a 10-point VAS).

One study [52] out of the four found a reduction of opioid intake as well as a decrease in pain scores for a few hours postoperative. Roytblat et al. [52] administrated a bolus dose of 0.15 mg/kg of ketamine and reported a 39.4% reduction of morphine consumption at 24 hours postoperative (ketamine = 29.5 mg vs placebo = 48.7 mg) and reduced VAS pain scores at 4 hours postoperative (ketamine = 1.1 vs placebo = 2.7 on a 10-cm VAS) but not 24 hours postoperative (ketamine = 0.5 vs placebo = 0.5).

Finally, the last study, Dahl et al. [54] studied the impact of pre or postincision administration of a bolus dose of 0.4 mg/kg. While they reported no difference in opioid consumption with either type of administration and no change in pain scores with the preincision administration, they found the postincision administration reduced VAS pain scores for 6 hours postoperative (ketamine = 31 vs placebo = 41 on a 100-mm VAS).

Efficacy of Low-Dose IV Infusion of Ketamine Reported in Clinical Trials: According to the Site Of Surgery

Data show that ketamine's potency as a postoperative analgesic can depend on the site of surgery, with ketamine proving to be efficacious for some sites and not for others [4]. This data can be difficult to interpret, however, as only one or two clinical trials have been conducted for the majority of surgical sites. In this section, we will detail the same 34 studies we discussed in the previous section (five studies are excluded due to their primary endpoints) as they relate to ketamine's efficacy by surgical site.

Ten sites of surgery were assessed by just one clinical trial. Among those sites, ketamine was reported to reduce both opioid consumption and pain scores for the following: appendectomy [53], cervical [32], and gastrectomy [47]. For five other sites, ketamine was reported to be effective in reducing opioid consumption but not pain scores. Those five sites were total hip surgery [31], laparotomy [21], colorectal [22], gynecologic laparoscopic surgery [40], and heart surgery [37]. Ketamine was reported not to have any effect in prostatectomy surgeries [24] or ear, nose, and throat surgeries [23].

Two studies [28,42] assessed ketamine in cruciate ligament repair surgery. Both studies reported a significant reduction of opioid consumption but no difference in pain scores with ketamine.

Results reported were mixed concerning patients undergoing a hysterectomy by two studies [46,54]. Dahl et al. [54] reported no difference in opioid consumption and reduced pain scores for only 6 hours postoperative in the ketamine group. Sen et al. [46] reported a significant reduced consumption of morphine for 24 hours postoperative with no reduction in pain scores.

Three studies assessed the administration of ketamine for renal surgery [25,27,49]. Two of these [25,27] reported a significant reduction of opioid consumption with no lasting effect on pain scores, while the third reported no effect with ketamine [49].

Two studies [36,38] conducted their clinical trial on total knee arthroplasty. Aveline et al. [38] reported that ketamine significantly decreased both opioid consumption and pain scores, while Adam et al. [36] reported a significant reduction only for opioid consumption.

For patients undergoing an open cholecystectomy, two studies [51,52] found ketamine to reduce both opioid consumption and pain scores (at least for a few hours).

Abdominal sites were assessed by six clinical trials [33,35,39,44,48,50]. Of the three [35,44,50] that studied patients undergoing a major abdominal surgery, all reported a reduction of both opioid consumption and pain scores (of at least a few hours) when administrating ketamine. Two trials assessing lower abdominal surgeries [33,39] achieved similar results. Concerning upper abdominal surgeries, however, Edwards et al. [48] reported that ketamine had neither an effect on opioid consumption nor pain scores.

Results concerning lumbar spine surgeries are mixed. Some studies reported that ketamine significantly reduced opioid consumption [26,30,34,43] and/or pain scores, while others reported no differences [29,32]. For example, Aveline et al. [43] reported a reduction of opioid consumption and pain scores for 6 hours postoperative with

ketamine, while Subramaniam et al. [29] and Yamauchi et al. [32] observed no such effect. Kim et al. [34] and Loftus et al. [26] reported a significant reduction of opioid consumption but no effect on pain scores with ketamine. Conversely, Urban et al. [30] found ketamine reduced pain scores but not opioid consumption.

Finally, two studies examined a mix of surgical sites [41,45]. For both studies, ketamine had no effect. As results were given for all sites together, however, no conclusion can be drawn from these two studies.

From these data, it appears that ketamine is more efficacious in managing postoperative pain for some sites of surgery (abdominal, open cholecystectomy) than others where little to no effect was reported (prostatectomy). Yet no definitive conclusions can be drawn from so few studies with such high heterogeneity. To better determine ketamine's efficacy with respect to particular surgical sites, future studies should assess different sites of surgery with the same ketamine regimen.

Safety of Low-Dose IV Ketamine

Safety for Different Routes of Administration of Ketamine According to the Meta-Analyses

Irrespective of the route, four meta-analyses out of five [12–14,20] concluded that ketamine was safe to be administrated as the drug did not increase the incidence of adverse side effects. In the meta-analysis that did find an elevated occurrence of side effects, they were all minor psychomimetic effects. Those effects were short term and reversible, ceasing when stopping the ketamine infusion or using benzodiazepine. Notably, the reviews reported ketamine had no impact on sedation scores. Instead, ketamine was found to decrease the incidence of nausea and vomiting.

Safety of Infusion Only According to the Clinical Trials

Two studies assessed a postoperative continuous infusion (without boluses) of low-dose ketamine [21,45]. Safety data are reported in Table 4. Both reported no major events and no differences in the incidence of minor adverse events (except a decrease in nausea when administering ketamine).

Safety of Continuous Infusion Following a Bolus Dose According to the Clinical Trials

Twenty-six clinical trials assessed a continuous IV infusion of low-dose ketamine following a bolus dose (with 25 reporting on adverse events). In these trials, the duration of infusion ranged from only intraop to 48 hours postoperative. Overall, it appears that, when used in a low-dose range (IV infusion rate less than 1.2 mg/kg/h), a continuous ketamine infusion is not associated with serious side effects (Tables 5, 6, 7 and 8). This conclusion is based on a total of 1,689 patients, 940 of whom received ketamine.

Only one study out of the 25 [24] reported serious adverse events (excessive bleeding in both the placebo and ketamine groups and an anaphylactic reaction in the ketamine group). Only two studies [37,49] out of 25 reported a minor side effect when administering ketamine. One found that ketamine increased the likelihood of short-term sedation during the first 24 hours [49], while the other observed that 8% of patients receiving the drug experienced transient hallucinations [37] ($P = 0.053$ between groups). Such symptoms, however, can be reversed by stopping the ketamine infusion or reducing its dose. In those two studies—which administered a 48-hour postoperative infusion of ketamine—safety does not appear to be related to the dose given; of the subset of studies that administered an infusion for 48 hours postoperative, these two used the lowest dosing regimen.

Table 4 Safety of postoperative infusion

		Number of Patients		Major Adverse Events	Minor Adverse Events			
							# of Patients Concerned	
Name of Study	Dose Used	Ketamine	Control	Y/N	Y/N	What Kind?	Ketamine	Control
Adriaenssens et al. [21]	2.5 mcg/kg/min (0.15 mg/kg/h)	15	15	No	Yes	Diplopia	2	0
						Dreams	1	1
						Secretion	1	0
						Nausea	1	6
						Vomiting	1	2
						Sedation	0	2
Barreveld et al. [45]	0.2 mg/kg/h	29	30	No	Yes	Hallucinations	1	0
						Pruritus	4	2

Table 5 Safety of intraoperative infusion

		Number of Patients		Major Adverse Events			Minor Adverse Events			
									# of Patients Concerned	
Name of Study	Dose Used	Ketamine	Control	Y/N			Y/N	What Kind?	Ketamine	Control
Aida et al. [47]	1 mg/kg + 0.5 mg/kg/h intraop	29	31	No information stated about adverse events						
De Kock et al. [19]	K2: 0.25 mg/kg bolus + 0.125 mg/kg/h infusion K3: 0.5 mg/kg bolus + 0.25 mg/kg/h infusion	40	20	No			Yes	Postoperative Nausea and Vomitiing (PONV)	No counts given (less than five episodes during 72 hours postop in 90% of patients)	
Ganne et al. [23]	0.15 mg/kg + 0.12 mg/kg/h	30	31	No			Yes	PONV	5	3
								Diplopia	1	0
								Nystagmus	0	3
								Involuntary movements	1	2
Guignard et al. [22]	0.15 mg/kg + 0.12 mg/kg/h until skin closure	25	25	No			Yes	PONV	4	5
Hadi et al. [17]	0.06 mg/kg/h intraop	15	15	No			Yes	PONV	5	8
Kararmaz et al. [25]	0.5 mg/kg bolus + 0.5 mg/kg/h	20	20	No			Yes	Nausea	1	6
								Pruritus	3	9
								Diplopia	3	0
								Dreams	2	1
Katz et al. [24]	0.2 mg/kg + 0.15 mg/kg/h	67	46	Yes	Keta	Ctrl	Yes	Agitation	1	1
								Vivid dreams	1	0
								Drowsiness	2	0
				Excessive bleeding	1	1		Alcohol withdrawal tremens	1	0
				Anaphylactic reaction	1	0		Hypotension/Bleeding	0	1
Loftus et al. [26]	0.5 mg/kg bolus + 10mcg/kg/min (0.6 mg/kg/h)	50	52	No			Yes	Nausea	22,50%	26,90%
								Vomiting	12,20%	15,40%
								Hallucinations	2,00%	2,00%
								Urinary Retention	2,00%	7,70%
Parikh et al. [27]	0.15 mg/kg + 0.12 mg/kg/h	30	30	No			Yes	PONV	0	4
Perrin and Purcell [15]	0.5 mg/kg Bolus + 4 mcg/kg/min infusion (0.24 mg/kg/h)	5	7	No			Yes	Psychotomimetic events	1	0
Sen et al. [46]	0.3 mg/kg + 0.05mg/kg/h	20	20	No			Yes	Dizziness	3	2
								Nausea	7	8
								Vomiting	7	8
								Somnolence	4	3
								Diarrhea	0	1
								Pruritus	2	1
								Constipation	1	0
								Dry mouth	4	3

Table 6 Safety of intraoperative and 2-hour postoperative infusion

		Number of Patients		Major Adverse Events	Minor Adverse Events			
							# of Patients Concerned	
Name of Study	Dose Used	Ketamine	Control	Y/N	Y/N	What Kind?	Ketamine	Control
Jaksch et al. [28]	0.5 mg/kg Bolus + 2 mcg/kg/h (0.02 mg/kg/h) 2 hours postop	15	15	No	Yes	Nausea	7	4
						Shivering	2	6
						Urinary retention	1	1
						Itching	0	1
						Disturbances	0	1
						Diplopia	1	0

Psychomimetic Events (Hallucinations, Dreams, and Diplopia). Out of the 10 studies using only an intraoperative infusion of ketamine that reported on safety, four [2,17,20,27] reported no psychomimetic events, while the remaining six [15,23–26,46] reported no difference in the incidence of those events between ketamine and placebo. Similarly, Jaksch et al. [28] reported no difference in the incidence of psychomimetic events following a 2-hour postoperative infusion of low-dose ketamine.

Out of the seven studies assessing a 24-hour postoperative IV infusion, one [17] reported no psychomimetic events and five [29–32,33] reported no differences between the ketamine and control groups. The last of these studies [48] reported a positive correlation between the incidence of vivid dreams and the dose of ketamine used. The authors assessed ketamine doses of 5 mg/h, 10 mg/h, and 20 mg/h. In the groups receiving 10 mg/h and 20 mg/h, two and five patients, respectively, exhibited vivid dreams. There were 10 patients per group, and no patients in the control group displayed these symptoms.

Out of the eight studies that assessed a 48-hour postoperative infusion, five [18,34–36,38] reported no psychomimetic events, while two [49,50] reported an equal incidence in both ketamine and placebo groups regarding hallucinations and unpleasant dreams. One study [37], as detailed above, reported an increase of hallucinations (of 8%) with ketamine.

Sedation. Sedation was increased in three studies out of 26, for duration of up to 15 minutes [22], 2 hours postoperative [25], and 24 hours postoperative [49].

Safety of Bolus Dose Only According to Clinical Trials

Eleven studies assessed the administration of an IV single dose or repeated boluses of ketamine during the intraoperative period (Table 9). With this regimen, ketamine was not associated with any serious side effects or any increase in the incidence of side effects. In fact, all 11 studies reported that there were no differences in the incidence of adverse events (nausea, vomiting, sedation, and psychomimetic events) when administering ketamine compared with placebo. Eight studies out of 11 [16,39,40,42,44,52–54] reported no psychomimetic events, and three studies [41,43,51] reported an equal incidence of those events in both ketamine and placebo groups. Sedation scores along with the incidence of nausea and vomiting were reported to be equal between ketamine and placebo groups for the 11 studies.

Liver Toxicity

In all of the 39 clinical trials included in our review, which assessed low-dose ketamine (IV infusion rate of less than 1.2 mg/kg/h and bolus dose less than 1 mg/kg), there were no indications of liver toxicity. Reports of liver toxicity have only been observed in abusers of ketamine or in chronic pain patients who received repeated and long doses of ketamine (two continuous IV 100-hour infusions of ketamine at an infusion rate of 10–20 mg/h) [55].

Long-Term Effect of Low-Dose IV Ketamine

Out of the 39 clinical trials that we reviewed, eight had a long-term follow-up. Six such studies [15,19,24,26,31,46] assessed continuous infusion with a bolus dose, and two [40,41] focused on only a single bolus of low-dose IV ketamine.

Out of the six intraoperative infusion studies, four reported that ketamine had a lasting improvement on pain [15,19,26,31]. At 6 weeks postoperative, Loftus et al. [26] found that patients who received an intraoperative infusion of 0.5 mg/kg + 0.6 mg/kg/h of ketamine had 26.2% less pain intensity and consumed 71% fewer opioids than patients treated with placebo. Additionally, patients receiving ketamine used antidepressants 10% less than those in the placebo group. The authors reported no difference in physical therapy needed or in adverse events between groups. Perrin and Purcell [15], using an intraoperative infusion of 0.5 mg/kg + 0.24 mg/kg/h of ketamine,

Table 7 Safety of intraoperative and 24 hours postoperative infusion

		Number of Patients		Major Adverse Events	Minor Adverse Events			
							# of Patients Concerned	
Name of Study	Dose Used	Ketamine	Control	Y/N	Y/N	What Kind?	Ketamine	Control
Edwards et al. [48]	1 mg/h morphine + 5mg/h Ketamine up to 24 hours postop	10	10	No	No			
	1 mg/h morphine + 10mg/h ketamine up to 24 hours postop	10		No	Yes	Vivid dreams	2	0
	1 mg/h morphine + 20 mg/h ketamine up to 24 hours postop	10		No	Yes	Vivid dreams	5	0
Hadi et al. [17]	0.06 mg/kg/h intraop	15	15	No	Yes	PONV	5	8
	0.06 mg/kg/h intraop + 24 hours	15	0	No	Yes	PONV	1	8
Remerand et al. [31]	0.5 mg/kg + 2mch/kg/min (0.12 mg/kg/h)	75	79	No	Yes	Pruritus	23%	17%
						Trouble with vision	17%	9%
						Urinary Retention	9%	10%
						Nightmares	9%	10%
						Pleasant dreams	9%	13%
						Hallucinations	8%	11%
Stessel et al. [33]	0.2 mg/kg + 0.12 mg/kg/h	17	18	No	Yes	Hallucinations	2	1
						Dysphoria	2	2
						Vivid dreams	3	2
						Combination	4	4
						Nausea	9	7
						Vomiting	7	6
						Pruritus	4	2
						Diplopia	9	5
Subramaniam et al. [29]	0.15 mg/kg bolus + 2 mcg/kg/min (0.12 mg/kg/h) continuous	15	15	No	Yes	Headache	0	2
						Dizziness	0	1
						Confusions	1	2
						Hallucinations	1	2
						Insomnia	0	1
						Anxiety	0	1
						Depression	0	1
						Excessive sedation	3	1
						Nausea	3	7
						Vomiting	0	1
						Pruritus	1	1
						Motor block	2	4
						Urinary Retention	0	1
						Hypotension/arrhythmia	0	1
Urban et al. [30]	0.2 mg/kg bolus + 2 mcg/kg/h (0.002 mg/kg/h) continuous	12	12	No	Yes	Confusions	2	1
						PONV	5	3
Yamauchi et al. [32]	1 mg/kg bolus + 42 mcg/kg/h (0.042 mg/kg/h) (= 1 mg/kg/24 hours)	64	67	No	Yes	Hallucinations	Same score,nocounts	
	1 mg/kg bolus + 83 mcg/kg/h (0.083 mg/kg/h) (= 2 mg/kg/24h)	72				PONV	Same score,nocounts	

Table 8 Safety of intraoperative and 48-hour postoperative infusion

		Number of Patients		Major Adverse Events	Minor Adverse Events			
							# of Patients Concerned	
Name of Study	Dose Used	Ketamine	Control	Y/N	Y/N	What kind?	Ketamine	Control
Adam et al. [36]	0.5 mg/kg + 3 mcg/kg/min (0.18 mg/kg/h) + 1.5 mcg/kg/min (0.09 mg/kg/h)	20	20	No	Yes	PONV	2	3
Aveline et al. [38]	0.2 mg/kg + 0.12 mg/kg/h intraop + 0.06 mg/kg/h for 48 hours postop	25	24	No	Yes	Urinary retention	2	3
						PONV	4	9
						Tachycardia	1	2
Ilkjaer et al. [49]	10 mg bolus + 10 mg/h 48 hours postop	24	28	No	Yes	Psychotomimetic events	2	1
						Unpleasant dreams	1	1
						Sedation scores higher with ketamine for 24 hours postop		
Lahtinen et al. [37]	0.075 mg/kg + 0.075 mg/kg/h	44	46	No	Yes	Hallucinations	4	0
						PONV	Same incidence no, info on counts	
Kim et al. [34]	0.5 mg/kg bolus + 1 mcg/kg/min (0.06 mg/kg/h)	18	17	No	Yes	Nausea	4	6
						Vomiting	1	1
						Dizziness	3	2
						Headache	3	1
						Sedation	0	1
	0.5 mg/kg bolus + 2 mcg/kg/min (0.12 mg/kg/h)	17	0	No	Yes	Nausea	6	6
						Vomiting	1	1
						Dizziness	4	2
						Headache	1	1
						Sedation	1	1
Stubhaug et al. [18]	0.5 mg/kg + 2 mcg/kg/min for 24 hours (0.12 mg/kg/h) + 1 mcg/kg/min (0.06 mg/kg/h) for 48hours	10	10	No	Yes	Vomiting	0	8
						Sedation	Same score, no counts	
						Nausea	Same score, no counts	
Webb et al. [50]	0.3 mg/kg + 0.1 mg/kg/h	56	64	No	Yes	Hallucinations	6	5
						Sedation	Scores reduced in ketamine	
Zakine et al. [35]	0.5 mg/kg bolus + 2 mcg/kg/min (0.12 mg/kg/h)	50	27	No	Yes	PONV	Same score, no counts	
						Sedation	Same score, no counts	

Table 9 Safety of single dose

		Number of Patients		Major Adverse Events	Minor Adverse Events			
							# of Patients Concerned	
Name of Study	Dose Used	Ketamine	Control	Y/N	Y/N	What Kind?	Ketamine	Control
Argiriadou et al. [44]	0.5 mg/kg + 0.2 mg/kg/20 minutes	15	15	No	Yes	Hypotension	1	2
						PONV	3	5
	0.5 mg/kg	15		No	Yes	PONV	4	5
Aveline et al. [43]	0.15 mg/kg (+0.1 mg/kg morphine) (compared with morphine alone 0.1 mg/kg)	23	23	No	Yes	Unpleasant dreams	1	0
						PONV	6	10
Behdad et al. [53]	0.5 mg/kg	40	40	No	No			
Dahl et al. [54]	0.4 mg/kg	60	29	No	Yes	Severe emetic symptoms	7	1
Dullenkopf et al. [41]	0.15 mg/kg	36	33	No	Yes	Diplopia	1	1
	0.5 mg/kg	41		No	Yes	Bad dreams	1	0
						Hallucinations	1	0
						Diplopia	1	1
Kafali et al. [39]	0.15 mg/kg	30	30	No	Yes	PONV	1	2
						Urinary retention	4	2
Kwok et al. [40]	0.15 mg/kg	90	45	No	Yes	PONV	Same incidence no, info on counts	
Menigaux et al. [42]	0.15 mg/kg	30	15	No	Yes	PONV	3	3
						Urinary retention	2	1
Roytblat et al. [52]	0.15 mg/kg	11	11	No	Yes	Nausea	2	2
						Vomiting	1	2
Safavi et al. [51]	1 mg/kg	30	30	No	Yes	Nausea	1	1
						Vomiting	2	1
						Dizziness	1	2
						Hallucinations	1	0
Xie et al. [16]	0.5 mg/kg	28	14	No	Yes	PONV	Five patients, no details for each group	

reported a higher improvement in pain scores in the ketamine group at 4 weeks postoperative (average improvement from preoperative ratings on the Womac Pain Scale was 5.2 points in the ketamine group compared with 1.4 in the placebo group). With the highest regimen, they assessed—0.5 mg/g/h + 0.25 mg/kg/h—De Kock et al. [19] found that patients who received ketamine had significantly less residual pain compared with those who received placebo at 2 weeks, 1 month, and 6 months postoperative. Similarly, Remerand et al. [31] reported that at 1 month, 3 months, and 6 months postoperative, fewer patients who received ketamine (intraoperative and 24-hour postoperative infusion equal to 0.5 mg/kg + 0.12 mg/kg/h) had persistent pain compared with those receiving placebo ($P = 0.008$). At 6 months postoperative, 21% of placebo patients had pain compared with 8% of ketamine patients. Furthermore, 56% of placebo patients needed help with walking (crutches or walking frame) compared with 31% of ketamine patients.

In contrast to the four aforementioned studies, Katz et al. [24] and Sen et al. [46] reported no differences in pain reduction among groups at 2 and 6 weeks postoperative, or at 1, 3, and 6 months, respectively.

Neither study that used a single dose of ketamine [40,41] reported a difference in pain management or in the recovery process between patients who received ketamine and patients who received placebo. Dullenkopf et al. [41] used a bolus dose of either 0.15 mg/kg or 0.5 mg/kg and assessed patients at 3 months postoperative, and Kwok et al. [40] used a bolus dose of 0.15 mg/kg and assessed patients at 7 days and 4 weeks postoperative.

From these results, it appears that ketamine's enduring impact on pain scores is related to its efficacy in the acute postoperative period when administered as a continuous infusion. In fact, among the six studies that used a continuous infusion of ketamine and assessed the agent's long-term effects, Katz et al. [24] and Sen et al. [46] were the only ones that reported no analgesic effect with ketamine in the postoperative period. By contrast, the four other studies [15,19,26,31] that showed ketamine to have a lasting impact found that it reduced both opioid consumption and pain scores for at least a few hours postoperative. From the two trials examining ketamine's long-term effects that used a bolus dose, there is no evidence that such a regimen has an impact on residual pain.

Experience at UPMC Shadyside and Presbyterian

At UPMC Shadyside and Presbyterian, low-dose IV infusion of ketamine has been added to the standard of care for postoperative analgesia in opioid-tolerant patients since June 2010. The regimen used is a 48-hour postoperative infusion of 5 mg/h administered via a Hospira pump (in continuous infusion mode). A pilot study was conducted to evaluate this new protocol at UPMC Presbyterian and Shadyside Hospitals and involved 27 patients (13 at Shadyside and 14 at Presbyterian). Data collected during this pilot study showed a reduction of mean VAS pain scores both at Presbyterian hospital (VAS pain scores prior to ketamine = 8 vs VAS pain scores after ketamine = 4) and Shadyside hospital (VAS pain scores prior to ketamine = 5 vs VAS pain scores after ketamine = 3). While a decrease of morphine consumption for patients treated at Presbyterian hospital (mean morphine consumption prior to ketamine = 54.4 mg/day vs 18.9 mg/day after ketamine) was reported, no differences in consumption were reported for patients at Shadyside hospital. Concerning safety, no events related to ketamine were reported at Presbyterian, while two hallucination events were reported at Shadyside.

Since the implementation of low-dose IV ketamine in the standard of care in June 2010, process measures and safety data have continued to be collected to ensure safety and improve the quality of ketamine's administration. Data were presented at the 8th Annual UPMC Update in Acute and Chronic Pain (Farmington, PA) in 2012. No serious adverse events or concerns were reported concerning the administration of ketamine. Out of the 146 patients that had been treated with ketamine at Presbyterian since June 2010, two patients experienced hallucinations, and two patients had respiratory depression. At Shadyside, out of 222 patients who received ketamine, only one patient experienced urinary retention.

Between June 2010 and February 2014, 1,082 chronic pain patients have been treated with low-dose infusion of ketamine for postoperative analgesia at UPMC hospitals. According to the pharmacy database, for those patients, the median amount of dose given was two bags of 30 mL with a concentration of ketamine equal to 5 mg/mL, and the mean was 2.97 bags with a 95% confidence interval of (2.81; 3.13). A double-blinded, placebo-controlled, clinical trial on the efficacy and safety of low-dose IV infusion of ketamine for chronic pain patients undergoing a back surgery should be conducted at UPMC. This clinical trial should confirm the observed results of an improvement of pain management with ketamine and further evaluate ketamine's analgesic properties.

Discussion

This review is the first one to focus only on continuous IV infusion or bolus dose of low-dose ketamine (infusion rate of less than 1.2 mg/kg/h with or without bolus dose of 1 mg/kg). From this review, several conclusions regarding the use of ketamine IV low infusions can be proposed. However, all should be interpreted with care as this is based on a small number of studies. A total of 39 studies were included in our review, 34 of which were used to assess ketamine's efficacy according to the regimen administered or site of surgery.

Based on this review, it is clear that ketamine reduces opioid consumption. For 23 of 34 studies, the mean reduction of opioid consumption with ketamine was 40%. Although the degree of opioid consumption tended to be correlated with the dose of ketamine administered, a clear

dose-related effect could not be drawn. The high heterogeneity among studies, including varying sites of surgery and intraoperative anesthetic management, made drawing a definitive conclusion about ketamine's dose-related effect difficult. Further studies should assess different doses of low-dose ketamine using the same protocol to confirm a correlation between the dose of ketamine administered and the magnitude of its analgesic effect.

Results regarding pain scores are not as clear as those for opioid consumption. Only eight studies out of 34 reported a significant reduction of pain scores of at least 24 hours postoperative. This could be due, at least in part, to the fact that only 10 studies out of 34 used reduction of pain scores (VAS or NRS) as the first statistical endpoint compared with 24 that used reduction of opioid consumption for this measure. For the majority of studies then, calculations for sample size and power were designed to detect a reduction in opioid consumption, not pain scores. Hence, the statistical criteria in most of the studies examined may not have been powerful enough to detect differences in pain scores. In fact, out the 24 studies that used reduction of opioid consumption as their first endpoint, only seven reported a significant reduction of pain scores for at least a few hours postoperative, while six out of the 10 studies that used pain scores as first endpoint reported a significant reduction.

Moreover, several other factors make interpreting results pertaining to pain scores challenging. Indeed, VAS pain scores reported in the clinical trials were low (<4), studies differed in the manner they assessed pain scores, and finally, pain scores are not the most functional measures of pain, as they are very subjective. Because reduction of opioid consumption is a more generalizable criterion, results concerning ketamine's opioid-sparing effect are therefore more useable than those regarding its impact on pain scores.

Lack of data makes it difficult to find a correlation between the site of surgery and the magnitude of ketamine's analgesic effect. Furthermore, even in the cases where several studies were conducted on a single site, there was significant variation in the protocol, dose, and length of infusion among trials.

Low-dose ketamine has a long-term effect on residual pain when administrated as an IV infusion (intraoperative only or intraoperative followed by a 24-hour postoperative infusion regimens have only been studied), not as a single dose. This effect seems to occur only when ketamine is efficacious during the postoperative period. Further studies should assess the long-term effect of ketamine as an improvement of pain was reported up to 6 months postoperative.

Data suggest that the combination of ketamine and morphine might increase the efficacy of ketamine. Aveline et al. [43] used a bolus dose of 0.15 mg/kg ketamine in conjunction with morphine and achieved a reduction of both opioid consumption and pain scores for up to 48 hours postoperative. This result differed from other studies that assessed a 0.15-mg/kg bolus and reported a significant reduction of opioid consumption and improved pain scores lasting only for a few hours postoperative. Further studies should assess the synergic effect of ketamine with other drugs used to treat pain.

Concerning safety, we reported results similar to previous reviews on ketamine [12–14,20]. The administration of ketamine was not associated with serious side effects or a significant increase in the likelihood of adverse events among the 2,482 patients we reviewed (1,403 of whom received ketamine).

Conclusions

Low-dose ketamine is clearly safe to administer and enhances postoperative analgesia. Our review tends to support the idea that ketamine's benefit predominantly comes from a reduction of opioid burden more than a reduction of pain scores. The drug's optimal dose and regimen of administration, however, remain unknown. To ascertain the dose and regimen at which ketamine is most effective, future studies could alter the length of intraoperative and postoperative infusions or use higher intraoperative doses.

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