SYSTEMATIC REVIEW

Intravenous ketamine in gynaecological surgeries reduces pain score and opioid consumption

Anwar ul Huda,[1] Raheel Minhas,[2] Mohammad Yasir[3]

Abstract

Objective: To assess the effect of intravenous ketamine on postoperative pain control, opioid consumption, and the incidence of postoperative adverse events in gynaecological surgeries.

Method: The systematic review and meta-analysis were conducted in July 2020 and the search was repeated in July 2021 to ensure accuracy. The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) as ID-CRD42020188637 in July 2020. The search, done on online databases Medline and Science Direct, comprised studies on patients who underwent general anaesthesia for gynaecological surgeries and received intravenous ketamine intraoperatively, and the findings included opioid consumption, postoperative pain control, and associated side-effects.

Results: Of the 79 randomised controlled trials found, 9 (11.4%) were subjected to meta-analysis. The use of intravenous ketamine reduced pain score at 2h (p=0.003) and 24h (p=0.002) postoperatively in gynaecological surgeries. In laparoscopic gynaecological surgeries, lower pain scores were reported at 1h (p=0.01) and 2h (p=0.002) postoperatively. Lower pain scores were reported at 24h postoperatively in open gynaecological surgeries (p=0.002). Intravenous ketamine increased the time to first-request analgesia postoperatively (p=0.03), and reduced postoperative 24h opioid consumption (p=0.002).

Conclusion: The use of intravenous ketamine significantly reduced postoperative pain at 2h and 24h after gynaecological surgeries and at 1h and 2h after laparoscopic gynaecological surgeries.

Keywords: Ketamine, Pain score, Gynaecological surgery, Opioid consumption.

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Introduction

Ketamine blocks central sensitisation of pain by inhibition of excitatory amino acids, such as glutamate.[1] In addition to its role as an intravenous (IV) anaesthetic agent, ketamine has anti-inflammatory, analgesic and anti-hyperalgesic properties.[2] Ketamine has been shown to improve perioperative analgesia when used at different dosages and routes with some adverse effects.[3] Although there are many meta-analyses published about the role of ketamine in providing analgesia in a variety of surgical procedures, its efficacy in gynaecological surgeries is still unknown.[4,5]

Pain associated with gynaecological surgery is a complex phenomenon with parietal and visceral components resulting from the activation of multiple pain mechanisms and pathways. As such, a multimodal analgesic regimen using both opioid and non-opioid agents seem to be a more optimal approach.[6]

The current systematic review and meta-analysis were planned to investigate the effect of the perioperative use of IV ketamine on postoperative pain scores, opioid consumption, and the incidence of adverse events like postoperative nausea and vomiting (PONV), pruritus and drowsiness.

Materials and Methods

The systematic review and meta-analysis were conducted in July 2020 and the search was repeated in July 2021 to ensure accuracy. The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) as ID-CRD42020188637 in July 2020. The search and review were done in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[7]

The search, done on online databases Medline and Science Direct, comprised randomised controlled trials (RCTs) published in English studies related to patients who underwent general anaesthesia for gynaecological surgeries and received IV ketamine intraoperatively, and the findings included opioid consumption, postoperative pain control, and associated side-effects. Both open and laparoscopic gynaecological surgeries were included. Any pre-incision IV ketamine regimen administered intraoperatively was accepted if the doses were defined clearly in the methodology.

The selected studies needed to have reported one of the two primary outcome measures; pain scores or reduction in opioid consumption in the early postoperative period. The early postoperative period was defined as the first 24h after surgery. The secondary outcome measures included the incidence of PONV, drowsiness, dizziness and pruritus within 24h post-surgery. Only primary research was considered for review, and abstracts, comments, review articles, and technique articles were excluded.

Data was extracted using a predesigned proforma regarding populations and outcomes from individual studies. It included information like studies' general details (Journal, year of publication, design, groups, and outcomes), study participants, sample size, intervention (dosages and timing of administration) and outcomes (pain score, opioids consumption, adverse events). Means and standard deviations of continuous data were extracted from the accompanying tables or graphs.

The search and the use of the Revised Cochrane risk-of-bias tool (RoB2)[8] were done by two researchers independently. During the entire process, all discrepancies were settled through discussion between the researchers. Both authors independently appraised the individual studies according to the Consolidated Standards of Reporting Trials (CONSORT) checklist.[9]

For meta-analysis of the included studies, Review Manager (RevMan for Mac, version 5.4; Cochrane Collaboration, Oxford, UK) was used. The heterogeneity of data was assessed by measuring I^2. Data on the pain assessment results at different time points and 24h opioid consumption were pooled. Side-effects were also pooled with no time points. For continuous data, the standardised mean difference was used to report the treatment effect, while odds ratios were used for dichotomous data. A random-effect model was used for the meta-analysis. $P<0.05$ was set as the level of statistical significance.

Results

Of the 79 RCTs found, 9 (11.4%) were subjected to meta-analysis (Figure-1). We used the pathway as recommended in RoB2 for risk of bias in individual studies. All the included RCTs were found to have low

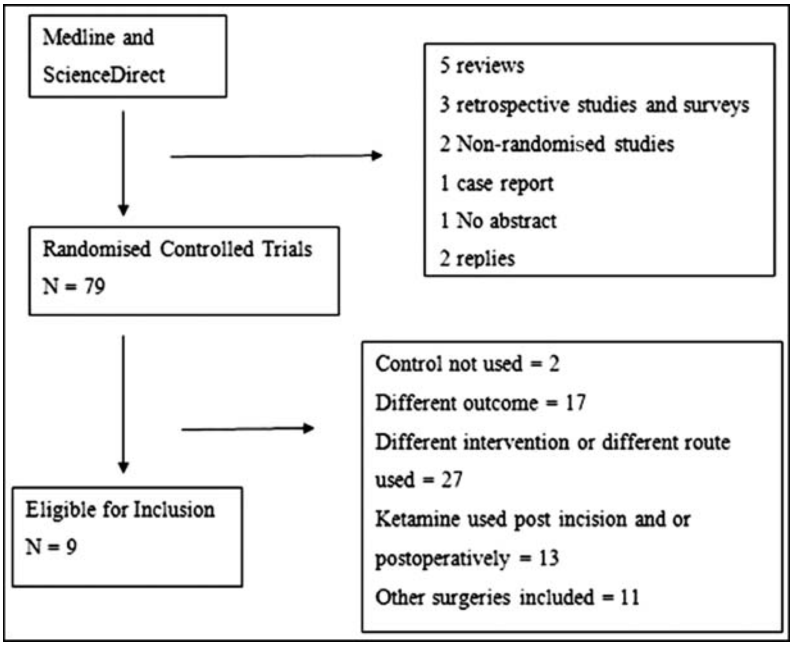

Figure-1: Flow diagram of the search process.

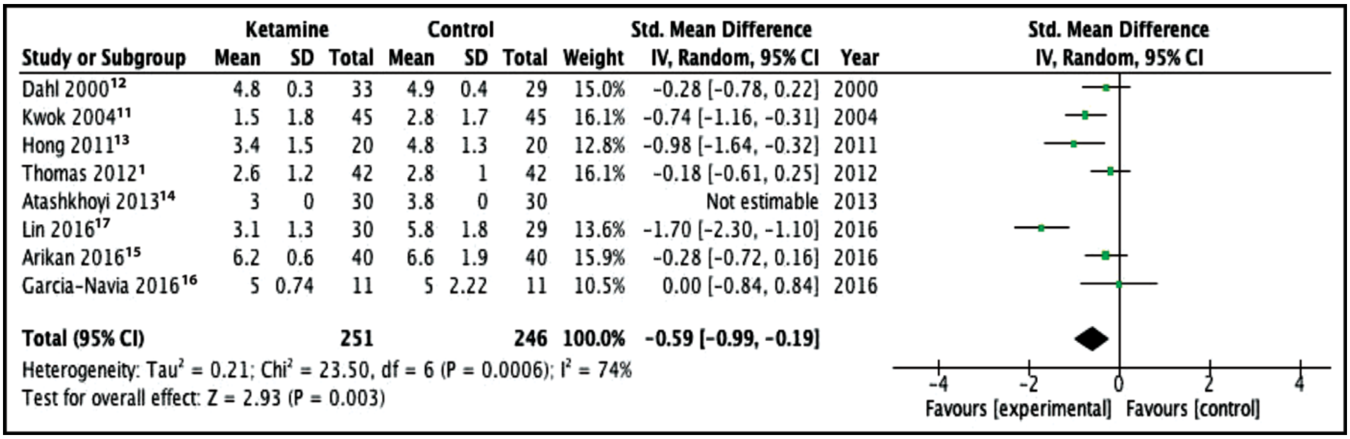

Figure-2A: Status 2 hours postoperatively.

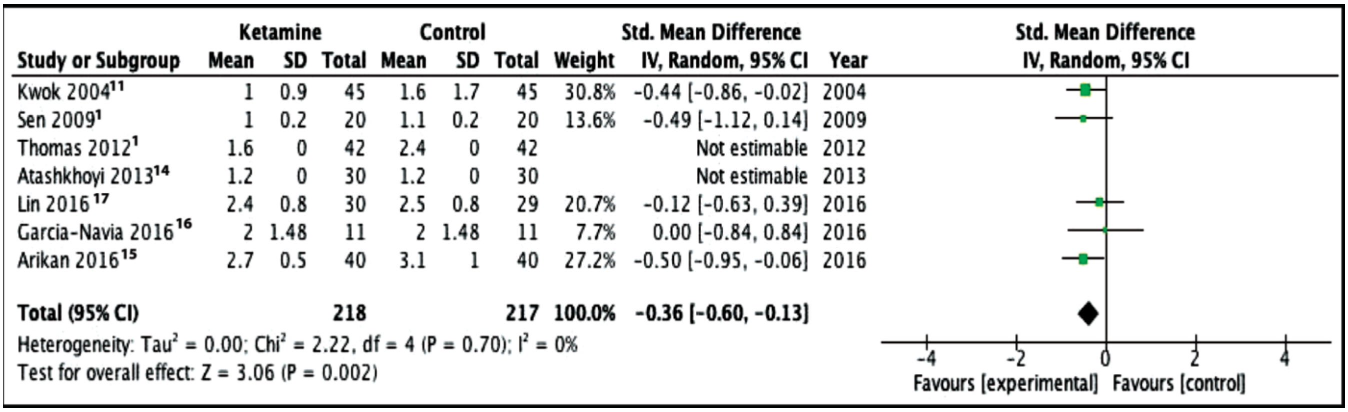

Figure-2B: Status 24 hours postoperatively.

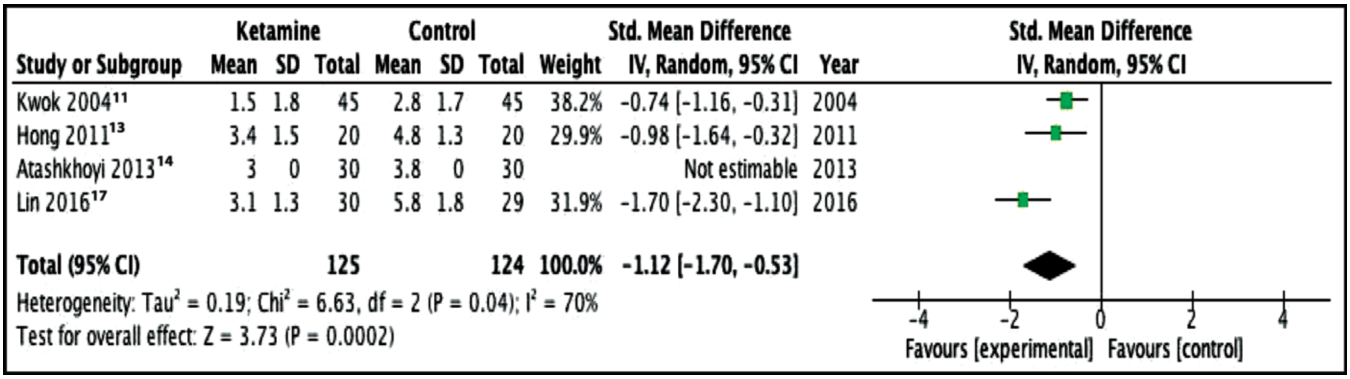

Figure-2C: Status 2 hours after laparoscopic gynaecological surgery.

risk of bias.

Dahl et al.[10] reported that there was no significant difference in pain scores between pre-incision ketamine group and control group up to 24h postoperatively. Kwok et al.[11] compared three groups of patients that underwent laparoscopic gynaecological surgery, and reported that the visual analogue scale (VAS) pain scores were significantly lower in the pre-incision ketamine group than in the control group during the first 6h postoperatively. Sen et al.[12] compared three groups of patients who underwent abdominal hysterectomy, and found that the verbal rating scale (VRS) scores were not significantly different between the ketamine and control groups 24h postoperatively. Hong et al.[13] found that IV ketamine resulted in lower VAS pain scores for the first 6h postoperatively. Thomas et al.[1] reported that the VAS pain scores were not significantly different between the ketamine and control groups at any time postoperatively. However, more patients (n=24, 64.3%) in the ketamine group reported no pain at 24h postoperatively compared to the placebo group (n=18, 42.9%; p=0.24). Atashkhoyi et al.[14] found that pain scores were significantly lower in the ketamine group for the first 3h postoperatively ($p<0.001$). In the post-anaesthesia care unit (PACU), 27% patients reported VAS score of ≤4 in the ketamine group compared to 100% in the control group. Arikan et al.[15] showed no significant difference in postoperative pain scores between ketamine and control groups. Garcia-Navia et al.[16] reported that the use of ketamine did not cause any significant difference in the VAS pain scores at rest from 0-24h postoperatively. Lin et al.[17] compared three groups, and VAS scores for visceral pain in group 3 (ketamine with skin infiltration) were significantly lower than those in group 2 (local infiltration only) and group 1 (placebo) at 2h and 6h postoperatively ($p<0.05$ and $p<0.01$, respectively). The VAS scores for incisional pain were not significantly different between groups 2 and 3 at 2h and 6h postoperatively, although these scores were significantly lower than those in group 1 ($p<0.01$).

A pooled meta-analysis of the included studies showed that the pain scores were significantly different between the ketamine and control groups at 2h and 24h postoperatively (p=0.003 and p=0.002, respectively) (Figures-2A and 2B). The pain scores at other time points (1h, 4h, 6h, 8h and 12h) were not statistically different between the groups ($p>0.05$). The subgroup meta-analysis of patients who underwent laparoscopic gynaecological surgery showed a significant difference in

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Sen 2009[1]	1	0.2	20	1.1	0.2	20	28.0%	-0.49 [-1.12, 0.14]	2009
Thomas 2012[1]	1.6	0	42	2.4	0	42		Not estimable	2012
Garcia-Navia 2016[16]	2	1.48	11	2	1.48	11	15.9%	0.00 [-0.84, 0.84]	2016
Arikan 2016[15]	2.7	0.5	40	3.1	1	40	56.1%	-0.50 [-0.95, -0.06]	2016
Total (95% CI)			**113**			**113**	**100.0%**	**-0.42 [-0.75, -0.08]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.14$, df = 2 (P = 0.56); $I^2 = 0\%$
Test for overall effect: Z = 2.46 (P = 0.01)

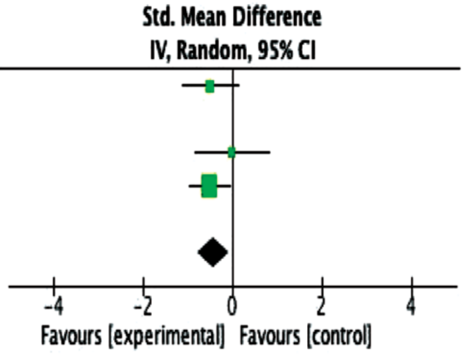

Figure-2D: Status 24 hours after open gynaecological surgery.

the pain scores at 1h and 2h postoperatively [p=0.01 and p=0.0002, respectively) (Figure-2C). Subgroup meta-analysis of patients having undergone open gynaecological surgeries showed a significant difference in pain scores at 24h postoperatively (p=0.01) (Figure-2D).

Kwok et al.[11] showed that the time to first-request analgesia in the pre-incision ketamine group (1.8h) was longer than that in the placebo group (0.7h) (p<0.001). Thomas et al.[1] did not find any significant difference between the two groups (p=0.54). However, more patients in the ketamine group received analgesia for >150min postoperatively compared to the placebo group (69.1% vs. 54.8%). Atashkhoyi et al.[14] reported that the time to first-request analgesia was significantly different between the two groups (17±8.5min vs. 165±28min; p<0.001). Lin et al.[17] reported that the time to first-request analgesia was significantly longer in the ketamine group than in the placebo group 113±14min vs. 28±8min; p<0.01).

A pooled meta-analysis of the included studies showed that the use of pre-incision ketamine resulted in a significant increase in the time to first-request analgesia in the postoperative period (p=0.03) (Figure-3A).

Dahl et al.[10] reported no significant difference in opioid requirements between pre groups. Kwok et al.[11] reported that the mean total morphine consumption in the ketamine group 1.5±2mg was less than that in the placebo group 3.4±2.7mg (p=0.003). Sen et al.[12] showed a significant decrease in 24h morphine consumption in the ketamine group 28±8mg compared to the placebo group 48±17mg (p<0.05). Thomas et al.[1] did not find any significant difference in the total morphine consumption between the ketamine 31.9±11.2mg and control 31.9±11.2mg groups (p=0.324). Atashkhoyi et al.[14] reported a significant difference in the total consumption of opioids in the postoperative period [tramadol 35±15mg versus 95±25mg (p<0.001). Arikan et al.[15] demonstrated a significant difference in opioid consumption between ketamine and control groups, 32.6±9.2mg and 65.7±8.2mg (p=0.015). Garcia-Navia et al.[16] did not find any significant difference in the 24h morphine consumption between ketamine 30.95±7.88mg and placebo 27.54±11.75mg groups. Lin et al.[17] did not find any significant difference in the postoperative meperidine consumption between the ketamine 54.2±16.4mg and control 52.5±14.5mg groups.

Pooled meta-analysis of the included studies showed that the use of IV ketamine intraoperatively for patients undergoing gynaecological surgeries resulted in a significant decrease in morphine-equivalent dose consumption in the postoperative period p=0.002 (Figure-3B). A 1:10 ratio of efficacy was used for the tramadol and meperidine doses versus morphine as Atashkhoyi et al.[14] used tramadol and Lin et al.[17] used meperidine in the postoperative period. Dahl et al.[10] used ketobemidone in the postoperative period which has same analgesic efficacy as morphine.

In terms of PONV incidence, only Garcia-Navia et al.[16] reported significant difference (p<0.05), while other included studies reported no significant difference between ketamine and control groups.

Pooled meta-analysis of the data did not demonstrate any statistically significant difference in the incidence of PONV between the ketamine and control groups (61 vs 65 episodes) (p=0.64).

In terms of drowsiness and pruritus, Sen et al.[12] reported 4(20%) incidences in the ketamine group and 3(15%) in the control group. Thomas et al.[1] reported 18(43%) incidences in the ketamine group and 20(47.6%) in the control group. Pooled meta-analysis did not demonstrate any significant difference in the incidence of drowsiness associated with the use of IV ketamine in gynaecological surgeries (p=0.84).

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Kwok 2004[11]	108	59.9135	45	42	39.9423	45	34.0%	1.29 [0.83, 1.74]	2004
Atashkhoyi 2013[14]	165	28	30	17	8.5	30	33.1%	7.06 [5.66, 8.46]	2013
Lin 2016[17]	113	14	30	28	8	29	33.0%	7.32 [5.86, 8.78]	2016
Total (95% CI)			**105**			**104**	**100.0%**	**5.18 [0.57, 9.80]**	

Heterogeneity: Tau² = 16.28; Chi² = 108.85, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.20 (P = 0.03)

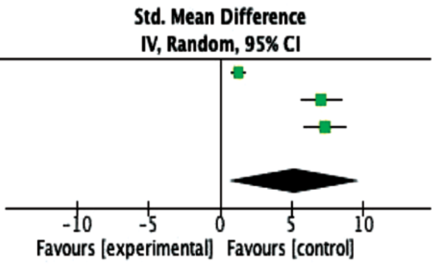

Figure-3A: Time to first-request analgesia.

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Dahl 2000[12]	18.8	6.4	33	20.4	8	29	12.8%	-0.22 [-0.72, 0.28]	2000
Kwok 2004[11]	1.5	2	45	3.4	2.7	45	13.0%	-0.79 [-1.22, -0.36]	2004
Sen 2009[1]	28	8	20	48	17	20	12.4%	-1.48 [-2.18, -0.77]	2009
Thomas 2012[1]	29.6	10.8	42	31.9	11.2	42	13.0%	-0.21 [-0.64, 0.22]	2012
Atashkhoyi 2013[14]	3.5	1.5	30	9.5	2.5	30	12.3%	-2.87 [-3.61, -2.14]	2013
Garcia-Navia 2016[16]	30.95	7.88	11	27.54	11.75	11	12.0%	0.33 [-0.51, 1.17]	2016
Lin 2016[17]	5.4	1.64	30	9.8	1.75	29	12.4%	-2.56 [-3.26, -1.86]	2016
Arikan 2016[15]	32.6	9.2	40	65.7	8.2	40	12.3%	-3.76 [-4.50, -3.02]	2016
Total (95% CI)			**251**			**246**	**100.0%**	**-1.43 [-2.34, -0.52]**	

Heterogeneity: Tau² = 1.61; Chi² = 131.31, df = 7 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.09 (P = 0.002)

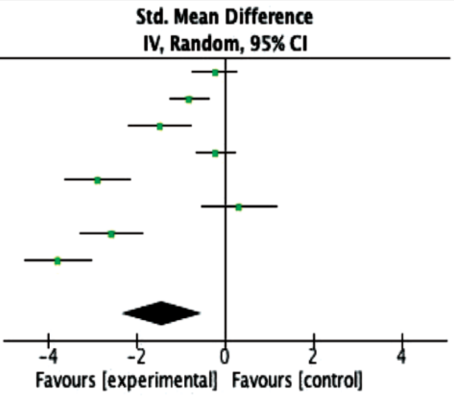

Figure-3B: Overall 24-hour opioid consumption.

Sen et al.[12] reported 2(10%) incidences of postoperative pruritus in the ketamine group and 3(15%) in the control group. Thomas et al.[1] reported 5(12%) pruritus cases in the ketamine group and 3(7%) in the control group. Arikan et al.[15] reported that none of patients had pruritus in the ketamine group while 5 (12.5%) patients complained of pruritus in the control group.

Pooled meta-analysis did not show any statistically significant difference in the incidence of postoperative pruritus (p=0.88).

Discussion

The current meta-analysis showed that IV ketamine resulted in better pain control at 2h and 24h after all types of gynaecological surgeries. It also resulted in better pain control at 1h and 2h after laparoscopic gynaecological surgery and at 24h in open open gynaecological surgeries. Bell et al.[18] also demonstrated that reduced VAS pain scores were reported for up to 24h postoperatively in 7 out of the 13 arms included in the review. In meta-analysis by Ye et al.[4] the pain scores were significantly better at 12h and 24h postoperatively with the use of IV ketamine cases of laparoscopic cholecystectomy. Pendi et al.[5] also reported lower postoperative pain scores in the ketamine group at 6h, 12h and 24h after spinal surgery. Li et al.[20] demonstrated in their meta-analysis that there were significant differences between the two groups regarding the pain scores within the first 24h postoperatively. Interestingly, contrary to the current findings, none of the previous reviews reported better pain scores at 1h or 2h postoperatively. There could be various reasons for this difference including dosage and timing of administration of ketamine and/or type of surgeries.

The current meta-analysis showed that the use of pre-incision ketamine resulted in a significant increase in the time to first-request analgesia in the postoperative period. This finding is consistent with the findings of Yang et al.[21] who showed that the time to first-request analgesia was significantly longer in the ketamine group than in the control group (p<0.00001).

The current results showed that the use of IV ketamine intraoperatively for patients undergoing gynaecological surgeries resulted in a significant decrease in opioid consumption in the postoperative period. This is consistent with the meta-analysis by Bell et al.[19] Ye et al.[5] also reported a significant difference in narcotic use at 24h between the groups (p=0.025). Li et al.[19] found ketamine to be effective in reducing cumulative morphine consumption during the early postoperative period after total knee arthroplasty. Pendi et al.[5] demonstrated that supplemental perioperative ketamine reduced postoperative opioid consumption up to 24h after spinal surgery. The current meta-analysis did not demonstrate any significant difference in the incidence of PONV between the ketamine and control groups. This is consistent with the findings reported by Elia et al.[21] On the other hand, meta-analyses by Li et al.,[19] Bell et al.,[18] Ye et al.[4] and Brinck et al.[2] found a significant reduction in the incidence of PONV in the ketamine group.

The current review did not find any significant difference in the incidence of drowsiness and pruritus between the two groups. Brinck et al.[2] also found no significant difference in this regard, but Ye et al.[4] reported that the incidence of pruritus in the ketamine group was significantly reduced for patients who underwent laparoscopic cholecystectomy ($p<0.05$).

The current meta-analysis has some limitations. Firstly, the dosages and timings of administration of IV ketamine were inconsistent. Dahl et al.[10] used 0.4mg/kg IV ketamine before the start of surgery. In the study by Kwok et al.[11] in the pre-incision group, IV ketamine 0.15mg/kg was administered before induction and normal saline after wound closure. In the postoperative group, patients received saline before induction, followed by ketamine 0.15mg/kg after wound closure. In the control group, patients received saline both before induction and after wound closure. In the study by Sen et al.[12] the control group received an oral placebo followed by an IV bolus and infusion of saline. The ketamine group received an oral placebo followed by 0.3mg/kg ketamine IV bolus before incision and then 0.05mg/kg/h infusion. The gabapentin group received oral gabapentin 1.2g followed by an IV bolus and infusion of saline. Hong et al.[13] used 0.3mg/kg IV ketamine at induction followed by 3mcg/kg/min infusion during laparoscopic gynaecological surgery. Thomas et al.[1] used 0.15mg/kg IV ketamine just before anaesthesia induction in patients undergoing elective gynaecological surgeries. Atashkhoyi et al.[14] used 0.5mg/kg IV ketamine at induction. Arikan et al.[15] used IV ketamine bolus 0.2mg/kg followed by infusion of 0.05mg/kg/h. Garcia-Navia et al.[16] used 0.5mg/kg IV ketamine 5min before the surgical incision. In the study by Lin et al.,[17] group 1 patients received IV normal saline only. In group 2, pre-incisional IV normal saline was administered, followed by local infiltration with ropivacaine at the end of the surgery. In group 3, patients received pre-incisional IV ketamine 0.3mg/kg and local skin infiltration with ropivacaine. Despite the differences in timing and dosing, all studies used IV ketamine as bolus at 0.15 to 0.5mg/kg. Also, all these boluses were administered before the surgical incision. In the current review, there was a difference in types of surgery as well. Of the total 9 studies, 4(44 %) were done laparoscopically and 5(55 %) were open surgeries. Another limitation is that all the studies did not report any delays in discharge or re-admission due to poor pain control, nausea or vomiting.

Conclusion

The use of IV ketamine significantly reduced postoperative pain at 2h and 24h after all types of gynaecological surgeries, and 1h and 2h after laparoscopic and 24h after open gynaecological surgeries. The time to first-request analgesia was significantly reduced with IV ketamine. IV ketamine also significantly reduced postoperative opioid consumption at 24h. There was no significant difference in the incidence of PONV and pruritis associated with the administration of IV ketamine.

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Conflict of Interest: None.

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