Systematic Review

Effect of S-ketamine on Postoperative Pain in Adults Post-Abdominal Surgery: A Systematic Review and Meta-analysis

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Free full manuscript: www.painphysicianjournal.com **Background:** S-ketamine is the S-enantiomer of ketamine, which exerts anesthetic and analgesic effects through noncompetitive antagonism of N-methyl-D-aspartate (NMDA) receptors.

Objective: We aimed to define the relative risk of post–abdominal surgery pain in adults who were administered perioperative S-ketamine.

Study Design: Systematic review and meta-analysis.

Methods: Two reviewers independently screened the articles from the titles and abstracts based on our eligibility criteria, evaluated the risk of bias by using the Cochrane Collaboration Risk of Bias tool in randomized controlled trials, and extracted the data from the included studies according to a prespecified protocol; any disagreements were solved by consultation. The level of certainty for the main results were evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system

Results: Of the 1,621 studies identified, 9 studies were included; they were published from 2004 through 2022. Only one study involved epidural anesthesia, whereas the other 8 studies included general anesthesia. The pain at rest scores at 4 and 24 hours post–abdominal surgery were significantly lower in the S-ketamine group, respectively. However, there was no significant difference between the 2 groups in the pain at rest scores at 48 hours post–abdominal surgery.

S-ketamine infusion reduced pain during movement 24 hours post-abdominal surgery, but not at 48 hours, respectively. The incidence of postoperative nausea and vomiting, as well as psychotomimetic adverse effects post-abdominal surgery were similar between the 2 groups, respectively. A subgroup analysis revealed that the pain at rest score at 4 hours post-abdominal surgery in patients in the intraoperative use group was remarkably reduced, compared with the patients who received S-ketamine perioperatively. Otherwise, the pain at rest score at 24 hours post-abdominal surgery in the perioperative use group was significantly reduced versus intraoperative use group.

Limitation: The number of trials included was small. The remarkable heterogeneity found in the pooled results at each time point post-abdominal surgery might affect the credibility of the results.

Conclusions: S-ketamine is effective in reducing the early postoperative pain of patients who received abdominal surgery, and may not increase the incidence of postoperative complications.

Key words: S-ketamine, intravenous, postoperative pain, abdominal surgery, pain scores, randomized controlled trial, systematic review, meta-analysis

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-ketamine is the S-enantiomer of ketamine, a well-known dissociative analgesic. The pharmacological characteristics of S-ketamine are similar to those of ketamine, and the affinity

of S-ketamine to N-methyl-D aspartic acid receptor (NMDA) is approximately double that of ketamine. For achieving the same anesthetic effect, the dosage of S-ketamine is only half of ketamine (1-4). High bioavailability and short clearance half-life make the anesthesia effect of S-ketamine more controllable. Besides, S-ketamine is associated with fewer psychotropic side effects compared with ketamine, and is gradually replacing ketamine for clinical use (5,6).

It has been suggested that S-ketamine is efficient to reduce opioid-induced hyperalgesia and tolerance, and reduce postoperative pain and opioid consumption (7), while some studies have reported that S-ketamine does not reduce the dosage of opioids, but significantly increases postoperative sedation (8). The only metaanalysis of acute postoperative pain in patients treated with S-ketamine showed that S-ketamine relieved postoperative pain and reduced the opioid demand of patients (9). However, their analysis only involved general anesthesia; no other form of anesthesia was included (9). The study provided a moderate-to-low level of certainty (9). As several new studies have been published on the perioperative use of S-ketamine in recent years (10,11), an updated systematic review and meta-analysis is necessary (12).

Abdominal surgery is one of the most common surgical procedures. A majority of patients undergoing abdominal surgery suffered from excruciating pain, which severely impeded the progress of postsurgery recovery, thus sufficient perioperative analgesia is crucial (13). S-ketamine is a potential therapy that may contribute to reduce postoperative pain post-abdominal surgery. Meanwhile, the incidence of anesthesia-related complications post-abdominal surgery is also higher (14,15). Whether the use of S-ketamine increases the incidence of postoperative adverse reactions remains to be discovered. We conducted a systematic review and metaanalysis of randomized controlled trials (RCTS) to evaluate the efficacy and safety of S-ketamine for analgesia in patients post-abdominal surgery.

METHODS

The protocol of our study was registered on the prospective register of systematic reviews (PROSPERO) with a registration number of CRD42021270703. We conducted this systematic review and meta-analysis according to the rules of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (16). The PRISMA checklist is shown in the supplementary materials (Supplemental Table 1).

Search Strategies

The PubMed, Cochrane Library, EMBASE and Web of Science databases were systematically searched for

RCTs published before December 2022 that investigated the influence of perioperative administration of S-ketamine for postoperative pain post-abdominal surgery. In addition, the reference lists of all included studies were all checked for any potential additional publications. Searches were run again just before the final analysis to find any further studies meeting the inclusion criteria. The detailed search strategies for each database are presented in the supplementary materials (Supplemental Table 2).

Inclusion and Exclusion Criteria

For a published article to be included in our study, it had to meet the following criteria: 1) the study is an RCT; 2) the influence of perioperative S-ketamine administration on postoperative pain post-abdominal surgery was investigated; 3) the surgeries were performed among adults (18 years or older); 4) the full text was available. Duplicate publications, reviews, editorials, abstracts, comments, case reports, meetings, or animal experiments were excluded.

Data Extraction and Quality Assessment

Two reviewers (MX and YL) independently screened the articles from the titles and abstracts based on our eligibility criteria, evaluated the risk of bias by using the Cochrane Collaboration Risk of Bias tool in RCTs, and extracted the data from the included studies according to a prespecified protocol with any disagreements solved by consultation.

The original data include the following characteristics: first author, country, publication year, sample size, age, intervention strategies and outcomes (postoperative pain scores and adverse events). A widely-accepted formula was used to estimate mean and SD from data described in the forms of median (interquartile range) (17). Since the exact values were not listed in some studies, and the authors only presented a graph, the related data were digitized by GetData Graph Digitizer v2.2.5 (GetData Pty Ltd, Kogarah, Australia) (18). In addition, we evaluated the level of certainty for the main results according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, and GRADEpro version 3.6 software (McMaster University) was used (Supplemental Table 3).

Data Synthesis

All analyses were performed using Review Manager (RevMan) Version 5.4. (the Nordic Cochrane Centre for the Cochrane Collaboration). The dichotomous variables were expressed as risk ratios (RRs) and 95% Cls, while the continuous variables were described in forms of mean difference (MD) and 95% Cls. Cochran's Q test and Higgins' I² statistical test were used to assess the statistical heterogeneity of the pooled results. Heterogeneity is defined as no, low, moderate, and high when I² values are 0%, 25%, 50%, and 75%. Subgroup analyses were performed based on the time point of S-ketamine administration. In addition, a sensitivity analysis was used to explore the sources of heterogeneity by excluding specific studies.

RESULTS

Study Selection

We identified 1,621 studies, of which 757 studies were duplicates and 846 studies were excluded by screening titles and abstracts. Then, 18 full-text articles were further screened, from which one study was excluded for not reporting outcomes and 8 studies were excluded for reporting on non-abdominal surgery. Finally, 9 studies (7,8,10-12,19-22) met the inclusion criteria and were included (Fig. 1). All involved articles were published between 2004 and 2022; the sample size ranged between 25 and 275.

The researchers assessed the analgesic effects of S-ketamine among patients undergoing abdominal surgery. Almost all studies reported the effect of S-

ketamine after general anesthesia (12), with one study exploring the effect of S-ketamine after epidural anesthesia (19). In the included studies, S-ketamine was used over different time ranges and at different dosages. Six articles reported intraoperative administration of S-ketamine(8,10,11,19,21,22), 2 articles reported the perioperative administration of S-ketamine (7,20), and one reported that S-ketamine was only administered postsurgery (12). The bolus doses varied from 0.25 to 0.5 mg/kg, and the doses of the infusions ranged between 0.12 and 0.3 mg/ kg/h. The detailed characteristics of the included studies are represented in Table 1.

Study Quality and Risk of Bias

The risk of bias assessment is summarized in Fig. 2. Nearly all the studies had a "low risk" or an "unclear risk." The GRADE assessment for the results are presented in Table S3. Funnel plots were symmetrical and suggested no evidence of publication bias (Supplemental Figs. 1-3).

Pain at Rest Scores Post-Abdominal Surgery

The results of the meta-analysis pooling indicates that the pain at rest scores at 4 and 24 hours postabdominal surgery were significantly lower in the Sketamine group (standardized mean difference [SMD] = -1.12; 95% Cl, -1.58 to -0.66; P < 0.00001; $I^2 = 91\%$; SMD = -0.37; 95% Cl, -0.59 to -0.15; P = 0.001; $I^2 = 57\%$) respectively. However, there was no obvious difference between the 2 groups for the pain at rest scores at 48 hours post-abdominal surgery (SMD = 0.05; 95% Cl,-0.69 to 0.78; P = 0.9; $I^2 = 96\%$). Additionally, substantial heterogeneity was found in the pooled results at each time point post-abdominal surgery ($I^2 > 50\%$) (Fig. 3).

Pain With Movement Scores Post-Abdominal Surgery

The present study indicates that S-ketamine infusion reduced pain with movement at 24 hours post-abdominal surgery, but not at 48 hours (SMD = -0.47; 95% CI, -0.67 to -0.26; P < 0.00001; $I^2 = 0\%$; SMD = -0.14; 95% CI, -0.50 to 0.21; P = 0.43; $I^2 = 74\%$) respectively (Fig. 4).

Postoperative Complications

As depicted in Fig. 5, the incidence of postoperative nausea and vomiting (PONV), as well as psychotomimetic adverse effects post-abdominal surgery were similar between the 2 groups (RR = 1.08; 95% CI, 0.88 to 1.33; P =



Standar	Country	Sample Size		Age (y)		Interventional strategy		
Study	country	S-ketamine	Control	S-ketamine	Control	Interventional strategy		
Argiriadou et al 2004	Greece	15/15	15	58 ± 13/64 ± 14	60 ± 10	0.5mg/kg IV before incision; 2. 0.5 mg/kg IV before incision + 0.2 mg/kg IV repeated at 20 min intervals until 30 min before the end of surgery		
Bornemann- Cimenti et al 2016	Austria	18/19	19	62.2 ± 9.8/ 58.4 ± 8.1	61.0 ± 12.4	Low-dose group: 0.25 mg/kg IV bolus after induction of anesthesia+0.125 mg/kg/h continuous IV for 48 h; 2. Minimal-dose group: 0.9% saline bolus after induction of anesthesia+0.015 mg/kg/h continuous IV infusion for 48 h		
Ithnin et al 2019	Singapore	45 44		48.1 ± 3.55	48.1 ± 4.86	0.25 mg/kg IV bolus before incision and after complete removal of uterus		
Miziara et al 2016	Brazil	21 21		18-65	18-65	S-ketamine 0.3 mg/kg/h before surgery and discontinued at the end of surgery		
Snijdelaar et al 2004	Netherlands	13	12	60.1 ± 4.7	61.7 ± 4.7	100 μg/kg IV bolus before surgery+intraoperative 0.12 mg/kg/h continuing IV+0.5 mg per bolus after surgery		
Xin et al 2022	China	120	118	27.25 ± 2.32	27.19 ± 1.21	Intraoperative S-ketamine 0.5 mg/kg/h		
Han et al 2022	China	122	153	31.64 ± 3.93	31.85 ± 4.16	Postoperative S-ketamine 0.5mg/kg as an adjuvant in PCIA		
Qiu et al 2022	China	92	91	41.2 ± 12.8	42.9 ± 10.5	Intraoperative S-ketamine 0.3 mg/kg/h		
Massoth et al 2021	Germany	76	76	38.1 ± 12.7	39.1 ± 12.7	Intraoperative dexmedetomidine 0.3 μg/kg/h and S-ketamine 0.15 mg/kg/h		

Table 1. Characteristics	s of	the	included	studies.
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Study	Control	Anesthesia	Postoperative	Type of surgery	Duration of anesthesia (1	min)	Duration of (min)	surgery	
		maintenance	analgesic		S-ketamine	Control	S-ketamine	Control	
Argiriadou et al 2004	Saline	GA+CEA	PCEA ropivacaine	Gastroenterological surgery, urological surgery, gynecological surgery	267.5 ± 24.5/ 269.5 ± 49.1	275.3 ± 40.9	248.4 ± 81.8/241.4 ± 90.0	224.5 ± 57.3	
Bornemann- Cimenti et al 2016	Saline	GA	PCIA piritramide	Open colorectal and hepatic surgery	NA	NA	183 ± 72/182 ± 71	189 ± 67	
Ithnin et al 2019	Saline	GA	PCIA morphine	Open gynecological surgery	134.0 ± 43.13	132.5 ± 37.65	NA	NA	
Miziara et al 2016	Saline	GA	Morphine iv	Laparoscopic cholecystectomy	NA	NA	NA	NA	
Snijdelaar et al 2004	Saline	GA	PCIA morphine + S-ketamine 0.5 mg per bolus	Radical prostatectomy	$132.5 \pm 37.65 \\ 134.0 \pm 43.13$	209.2 ± 89.7	148 ± 23	158 ± 25	
Xin et al 2022	Fentanyl 0.5 mg/(kg/h)	GA	NA	Obstetric surgery	NA	NA	186.85 ± 22.85	181.52 ± 23.58	
Han et al 2022	Saline	SA	PCIA S-ketamine 0.5mg/ kg+sufentanil 2µg/ kg+tropisetron 10mg, 2ml/h for 48h	Obstetric surgery	NA	NA	53.60 ± 9.99	51.59 ± 11.07	
Qiu et al 2022	Saline	GA	PCIA hydromorphone	Gynecological laparoscopy	121 ± 31.6	114.6 ± 39.9	96.4 ± 32.4	88.9 ± 35.4	
Massoth et al 2021	Repetitive bolus of sufentanil of 0.15 µg/kg	GA	PCIA morphine	Gynecological laparoscopy	151 ± 64.2	154.3 ± 59.5	81.3 ± 49.6	99.1 ± 62.7	

GA, general anesthesia; CEA, continuous epidural anesthesia; PCEA, patient-controlled epidural analgesia; IV, intravenous; NA, not applicable.

0.47; l² = 19%; RR = 1.3; 95% Cl, 0.87 to 1.94; *P* = 0.2; l² = 0%), respectively.

Subgroup Analysis

Since different time points of S-ketamine administration was likely to affect the outcomes, we further performed a subgroup analysis. We defined continuous intraoperative and postoperative use of S-ketamine as perioperative use. Subgroup analyses indicated that the pain at rest score at 4 hours post-abdominal surgery in the intraoperative use group was remarkably reduced (SMD = -1.71; 95% CI, -2.64 to -0.78; P = 0.0003; $I^2 = 95\%$), compared with the patients who received Sketamine perioperatively (SMD = -0.78; 95% CI, -1.93 to 0.37; P = 0.19; $I^2 = 76\%$). Otherwise, the pain at rest score at 24 hours post-abdominal surgery in the perioperative use group was significantly decreased (SMD = -0.53; 95% Cl, -0.81 to -0.24; P = 0.0003, I² = 0%) compared with the intraoperative use group (SMD = -0.18; 95% CI, -0.59 to 0.23; P = 0.4; I² = 69%). No significant difference of the pain at rest scores at 48 hours postabdominal surgery was observed between the 2 groups (Fig. 6). A subgroup analysis of pain with movement scores was not conducted because the number of stud-

ies was too small for reliable estimation.

Sensitivity Analysis

heterogene-The ity of the pain at rest score at 24 hours postabdominal surgery and the pain with movement score at 48 hours post-abdominal surgery were significantly decreased when excluding the study by Massoth et al (8) or the study by Snijdelaar et al (20) (SMD = -0.48; 95% CI, -0.64 to -0.31; P < 0.00001; $I^2 = 23\%$; SMD = -0.3; 95% Cl, -0.5 to -0.11; P = 0.002; l² = 33%), respectively (Fig. S4).



DISCUSSION

In the present study, we demonstrate

Fig. 3. Forest plot of postoperative pain scores in patients at rest after abdominal surgery. A. 4 hours postsurgery; B. 24 hours postsurgery; C. 48 hours postsurgery.





А							
	S-ketan	nine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Argiriadou 2004	7	30	5	15	6.0%	0.70 [0.27, 1.84]	
Han 2022	17	122	18	153	14.4%	1.18 [0.64, 2.20]	
Ithnin 2019	31	45	20	44	18.2%	1.52 [1.04, 2.21]	
Massoth 2021	26	76	33	76	29.7%	0.79 [0.53, 1.18]	
Miziara 2016	1	21	2	21	1.8%	0.50 [0.05, 5.10]	
Qiu 2022	34	92	27	91	24.4%	1.25 [0.82, 1.88]	
Xin 2022	5	120	6	118	5.4%	0.82 [0.26, 2.61]	
Total (95% CI)		506		518	100.0%	1.08 [0.88, 1.33]	•
Total events	121		111				
Heterogeneity: Chi ² =	7.37, df =	6 (P = 1	0.29); I ^z =	19%			
Test for overall effect:	Z = 0.73 (P = 0.4	7)				U.U1 U.1 1 1U 1UU
D							Favours [S-Retainine] Favours [Control]
D	S.ketan	nine	Contr	ol		Risk Ratio	Risk Ratio
Study or Subaroup	Events	Total	Events	Total	Weight	M-H Fixed 95% CL	M.H. Fixed, 95% Cl
Han 2022	28	122	24	153	60.2%	1 46 0 90 2 391	+
Ithnin 2019	20	45	1	44	2.9%	1 96 [0 18 20 80]	
Miziara 2016	1	21	0	21	1 4%	3 00 10 13 69 70	
Qiu 2022	9	92	12	91	34.1%	0.74 [0.33, 1.67]	
Snijdelaar 2004	2	13	0	12	1.5%	4.64 [0.25, 87.91]	
Total (95% CI)		293		321	100.0%	1.30 [0.87, 1.94]	•
Total events	42		37				
Heterogeneity: Chi ² =	315 df=	4 (P = 1	1 53) IF =	0%			
Test for overall effect:	7 = 1.28 (P = 0.2	0)	0.10			0.01 0.1 1 10 100
restion overall ellect.		- 0.2	.,				Favours [S-ketamine] Favours [Control]

Fig. 4. Forest plot of postoperative complications in patients after abdominal surgery. A) Postoperative nausea and vomiting. B) Psychotomimetic adverse events.

Δ		S-ke	etami	ne	Co	ontrol			Mean Difference	Mean Difference					
~	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl					
	Bornemann-Cimenti 2016	2.9	0.4	37	3.3	0.5	19	63.8%	-0.40 [-0.66, -0.14]	=					
	Qiu 2022	3.4	0.8	92	4	1.5	91	35.2%	-0.60 [-0.95, -0.25]	-8-					
	Snijdelaar 2004	2.7	2.5	13	2.8	2.6	12	1.1%	-0.10 [-2.10, 1.90]						
	Total (95% CI)	142					100.0%	-0.47 [-0.67, -0.26]	•						
	Heterogeneity: Tau ² = 0.00;	94, df	= 2 (P :	= 0.62);	$ ^2 = 0$	%									
	Test for overall effect: Z = 4.4	42 (P < 0.	0000	1)						-4 -2 U 2 4					
-										Favours (S-ketamine) Favours (Control)					
3		S-ke	tami	ne	Co	ontrol			Mean Difference	Mean Difference					
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV. Random, 95% CI					
	Bornemann-Cimenti 2016 2.5 0.4 37 2.9 0.4 19 41.79 Qiu 2022 2.4 0.8 92 2.6 0.8 91 41.09								-0.40 [-0.62, -0.18]	*					
									-0.20 [-0.43, 0.03]	-					
	Snijdelaar 2004 1.1 1.2 13 0.5							17.3%	0.60 [-0.09, 1.29]						
	Total (95% CI)			142			-0.14 [-0.50, 0.21]	•							
	Heterogeneity: Tau ² = 0.07; Chi ² = 7.75, df = 2 (P = 0.02); l ² = 74%														
	Test for overall effect: Z = 0.3	79 (P = 0.	43)						-4 -2 U 2 4						
										Favours (S-ketamine) Favours (Control)					
										Favours (S-Ketannine) Favours (Connoi)					

of the surgical stress response which is undesirable for a patient's recovery. Effective postsurgical pain management improves postoperative rehabilitation and enhances recovery. The results of our metaanalysis indicated that the pain at rest scores at 4 hours and 24 hours post-abdominal surgery were significantly lower in the S-ketamine group, but there was

that S-ketamine significantly lowers postoperative pain scores post-abdominal surgery. Specifically, the pain at rest scores at 4 and 24 hours, as well as the pain with movement score at 24 hours post-abdominal surgery were reduced in the S-ketamine group. In addition, S-ketamine did not increase the risk of PONV or psychotomimetic adverse events post-abdominal surgery.

Postoperative pain may lead to various aspects

no detectable difference between the 2 groups for the pain at rest score and the pain with movement score at 48 hours post-abdominal surgery.

In the subgroup analysis, the pain at rest score at 24 hours post-abdominal surgery in the perioperative use group was significantly reduced compared to the patients who received S-ketamine only intraoperatively. These results are consistent with the study Wang X

-		S-ke	etamin	e	c	ontrol			Mean Difference	Mean Difference
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
	6.1.1 Intraoperative use									
	Ithnin 2019	1.9	0.7	45	2.5	0.7	44	23.7%	-0.60 [-0.89, -0.31]	<u> </u>
	Miziara 2016	1.3	1.6	21	5.7	2.1	21	14.3%	-4.40 [-5.53, -3.27]	
	Xin 2022	2.85	0.62	120	3.91	0.81	118	24.3%	-1.06 [-1.24, -0.88]	*
	Subtotal (95% CI)	0.617 - 41		180	- 0.000	041-17	183	62.3%	-1.71[-2.04, -0.78]	
	Test for overall effect: Z = 3.6	51 (P = 0.)	50, df .0003)	= 2 (P	< 0.000	101); 1-	= 95%			
	6.1.2 Perioperative use		0.6	07	0.7		40	22.20	0.001.000.000	
	Bornemann-Cimenti 2016	2.4	0.6	37	2.7	0.6	19	23.3%	-0.30 [-0.63, 0.03]	
	Subtotal (95% CI)	1.4	1.2	13	2.9	1.0	31	14.4%	-1.50 [-2.62, -0.38]	
	Heterogeneity: Tau ² = 0.54; C Test for overall effect: $Z = 1.3$	Chi ² = 4.0 32 (P = 0.	08, df= .19)	: 1 (P =	0.04); I	² = 76	%	51.170	-0.70 [- 1.33, 0.37]	
	Total (95% CI)			236			214	100.0%	-1.31 [-1.97, -0.66]	•
	Heterogeneity: Tau ² = 0.45; (Chi ² = 57	.50. df	= 4 (P	< 0.000	101); P	= 93%			
	Test for overall effect: Z = 3.9 Test for subgroup difference	34 (P < 0.	.0001)	df = 1 ($P = 0.2^{\circ}$	2) I ² =	34 7%			-4 -2 0 2 Favours [S-ketamine] Favours [Control]
	Test for suburous uncrence		1.55.	ui – 1 (- 0.2	27.1 -	54.170			
_	Study or Subgroup	S-ke Mean	etamin SD	e Total	C Mean	ontrol SD	Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV, Random, 95% Cl
	9.1.1 Intraoperative use									
	Argiriadou 2004	3.57	0.69	30	3.92	0.71	15	18.4%	-0.35 [-0.79, 0.09]	
	Ithnin 2019	3.4	1.8	45	3	1.9	44	9.9%	0.40 [-0.37, 1.17]	+
	Massoth 2021	3.1	1	76	3	1.5	76	19.5%	0.10 [-0.31, 0.51]	+-
	Qiu 2022	2	1.5	92	2.6	0.8	91	21.6%	-0.60 [-0.95, -0.25]	
	Subtotal (95% CI)			243			226	69.4%	-0.18 [-0.59, 0.23]	•
	Heterogeneity: Tau ² = 0.12; 0 Test for overall effect: Z = 0.8	Chi ² = 9.6 35 (P = 0.	69, df = .40)	: 3 (P =	0.02); I	r = 69°	%			
	9.1.2 Perioperative use									
	Bornemann-Cimenti 2016	1.5	0.4	37	2	0.6	19	23.4%	-0.50 [-0.80, -0.20]	
	Snijdelaar 2004	1.2	1	13	2	1.4	12	7.2%	-0.80 [-1.76, 0.16]	
	Subtotal (95% CI)			50			31	30.6%	-0.53 [-0.81, -0.24]	· · · · · • • · · · · · · · · · · · · ·
	Heterogeneity: Tau ² = 0.00; 0 Test for overall effect: Z = 3.6	Chi ² = 0.3 51 (P = 0.	34, df = .0003)	: 1 (P =	0.56); I	² = 0%	,			
	Total (95% CI)			293			257	100.0%	-0.31 [-0.60, -0.02]	▲
	Heterogeneity: Tau ² = 0.07; (Chi ² = 12	.18, df	= 5 (P	= 0.03);	² = 59	9%			-4 -2 0 2
	Test for overall effect: Z = 2.0 Test for subaroup difference)7 (P = 0. s: Chi ² =	.04) : 1.86.	df=1 (P = 0.13	7). I²=	46.2%			Favours [S-ketamine] Favours [Control]
;		S-ke	etamin	е	Co	ntrol		1	Mean Difference	Mean Difference
_	Study or Subgroup	Mean	SD	Total	Mean	SD 1	fotal N	Weight I	V, Random, 95% Cl	IV, Random, 95% Cl
	10.1.1 Intraoperative use									
	Massoth 2021	3.1	1.1	76	2.1	1	76	25.3%	1.00 [0.67, 1.33]	
	Qiu 2022	1.4	0.8	92	1.4	0.8	91	26.1%	0.00 [-0.23, 0.23]	+
	Subtotal (95% CI)			168			167	51.4%	0.49 [-0.49, 1.47]	
	Heterogeneity: Tau ² = 0.48; 0 Test for overall effect: Z = 0.9	Chi ² = 23 39 (P = 0.	.22, df .32)	= 1 (P	< 0.000	101); I ^z	= 96%			
	10.1.2 Perioperative use	-	0.3	37	1.7	0.4	19	26.2%	-0.70 [-0.90, -0.50]	
	10.1.2 Perioperative use Bornemann-Cimenti 2016	1		13	0.9	0.8	12	22.4%	-0.10 [-0.73, 0.53]	
	10.1.2 Perioperative use Bornemann-Cimenti 2016 Snijdelaar 2004	1 0.8	0.8				31	48.6%	-0.48 [-1.05, 0.09]	
	10.1.2 Perioperative use Bornemann-Cimenti 2016 Snijdelaar 2004 Subtotal (95% CI)	1 0.8	0.8	50			~			
	10.1.2 Perioperative use Bornemann-Cimenti 2016 Snijdelaar 2004 Subtotal (95% CI) Heterogeneity: Tau ² = 0.12; (Test for overall effect: Z = 1.6	1 0.8 Chi ² = 3.1 34 (P = 0.	0.8 17,df= .10)	50 = 1 (P =	0.07); I	² = 68 ⁴	%			
	10.1.2 Perioperative use Bornemann-Cimenti 2016 Snijdelaar 2004 Subtotal (95% CI) Heterogeneity: Tau ² = 0.12; C Test for overall effect: $Z = 1.6$ Total (95% CI)	1 0.8 Chi² = 3.1 34 (P = 0.	0.8 17, df= .10)	50 = 1 (P = 218	0.07);	²= 68°	% 198 ·	100.0%	0.05 [.0.69 0 78]	-
	10.1.2 Perioperative use Bornemann-Cimenti 2016 Snijdelaar 2004 Subtotal (95% CI) Heterogeneity: Tau ² = 0.12; (Test for overall effect: Z = 1.6 Total (95% CI) Heterogeneity: Tau ² = 0.52; (1 0.8 Chi² = 3.5 34 (P = 0. Chi² = 7.4	0.8 17, df= .10)	50 = 1 (P = 218 = 3 (P	0.07); I	1 ² = 68 ⁴	* 198 *	100.0%	0.05 [-0.69, 0.78]	+
	10.1.2 Perioperative use Bornemann-Cimenti 2016 Snijdelaar 2004 Subtotal (95% CI) Heterogeneity: Tau ² = 0.12; (Test for overall effect: Z = 1.6 Total (95% CI) Heterogeneity: Tau ² = 0.53; (Test for overall effect Z = 0.1	1 0.8 Chi ² = 3.1 34 (P = 0. Chi ² = 74	0.8 17, df= .10) .98, df .90)	50 = 1 (P = 218 = 3 (P	0.07); I < 0.000	² = 684	* 198 = 96%	100.0%	0.05 [-0.69, 0.78]	4 -2 0 2
	10.1.2 Perioperative use Bornemann-Cimenti 2016 Snijdelaar 2004 Subtotal (95% CI) Heterogeneity: Tau ² = 0.12; (Total (95% CI) Heterogeneity: Tau ² = 0.53; (Test for overall effect: Z = 0.1 Test for subgroun difference	1 0.8 Chi ² = 3.1 34 (P = 0. Chi ² = 74 13 (P = 0. s: Chi ² =	0.8 17, df = .10) .98, df .90) : 2.81	50 = 1 (P = 218 = 3 (P	0.07); I < 0.000 P = 0.04	² = 684 01); ² 9), ² =	198 = 96% 64.4%	100.0%	0.05 [-0.69, 0.78] 	4 -2 0 2 4 Favours [S-ketamine] Favours [Control]
	10.1.2 Perioperative use Bornemann-Cimenti 2016 Snijdelaar 2004 Subtotal (95% CI) Heterogeneity: Tau ² = 0.12; (Total (95% CI) Heterogeneity: Tau ² = 0.53; (Test for overall effect: $Z = 0.1$ Test for overall effect: $Z = 0.1$	1 0.8 Chi ² = 3.1 34 (P = 0. Chi ² = 74 13 (P = 0. s: Chi ² =	0.8 17, df = .10) .98, df .90) : 2.81.	50 = 1 (P = 218 = 3 (P df = 1 (0.07); I < 0.000 P = 0.09	1 ² = 68 101); 1 ² 9). 1 ² =	% 198 = 96% 64.4%	100.0%	0.05 [-0.69, 0.78] 	4 -2 0 2 Favours [S-ketamine] Favours [Control]
	10.1.2 Perioperative use Bornemann-Cimenti 2016 Snijdelaar 2004 Subtotal (95% CI) Heterogeneity: Tau ² = 0.12; (Total (95% CI) Heterogeneity: Tau ² = 0.53; (Test for overall effect: $Z = 0.1$ Test for suboroup difference	1 0.8 Chi ² = 3.1 34 (P = 0. Chi ² = 74 13 (P = 0. Is: Chi ² =	0.8 17, df= .10) .98, df .90) : 2.81.	50 = 1 (P = 218 = 3 (P df = 1 (0.07); I < 0.000 P = 0.09	² = 684 101); ² 9). ² =	% 198 = 96% 64.4%	100.0%	0.05 [-0.69, 0.78] 	4 -2 0 2 Favours [S-ketamine] Favours [Control]
	10.1.2 Perioperative use Bornemann-Cimenti 2016 Snijdelaar 2004 Subtotal (95% CI) Heterogeneity: Tau ² = 0.12; (Test for overall effect: Z = 1.6 Total (95% CI) Heterogeneity: Tau ² = 0.53; (Test for overall effect: Z = 0.1 Test for subaroup difference	1 0.8 Chi ² = 3.1 34 (P = 0. Chi ² = 74 13 (P = 0. s: Chi ² =	0.8 17, df= .10) I.98, df .90) : 2.81.	50 = 1 (P = 218 = 3 (P df = 1 (0.07); I < 0.000 P = 0.09	1² = 684 101); 1² 9). 1² =	% 198 = 96% 64.4%	100.0%	0.05 [-0.69, 0.78] 	4 -2 0 2 Favours [S-ketamine] Favours [Control]

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et al (9). However, some studies did not distinguish the pain at rest scores and the pain with movement scores clearly, so we compared the studies that specified the type of pain score. Some studies did not record pain scores at 12 hours, so we only compared 3 time points: 4 hours, 24 hours, and 48 hours.

In the subgroup analysis, the pain at rest score at 4 hours post-abdominal surgery in the intraoperative use of S-ketamine group was remarkably reduced compared to the perioperative use group. In fact, the dose of intraoperative infusion of S-ketamine in the perioperative use group was significantly lower, compared with the intraoperative use group. As pain relief is dose-dependent, S-ketamine in the intraoperative use group might provide longer and effective analgesia in the postoperative period, thus resulting in a lower pain score in the perioperative use group at 4 hours postsurgery.

Early postoperative ambulation contributes to the rapid recovery of intestinal function, which is especially necessary for patients post-abdominal surgery (23). In this systematic review and meta-analysis, we showed that S-ketamine significantly reduced the pain with movement score at 24 hours, but not at 48 hours postabdominal surgery, but this result differed from Wang's study (9). We considered the possibility that the involved studies reporting different administration methods of S-ketamine contributed to the discrepancies.

In addition, severe postoperative pain may result in increased postoperative analgesics consumption. However, we did not analyze postoperative analgesics consumption in the present study. It is worth noting that different types of surgery lead to different degrees of pain. Furthermore, the criteria of postoperative analgesic interventions for anesthesiologists varies among different institutions, thus the consumption of opioids may not be a reliable indicator for evaluating the analgesic effects of drugs in the perioperative period (24).

The use of S-ketamine in abdominal surgery did not increase the risk of either PONV or psychotomimetic adverse events. It is important to mention that sedatives were used in almost all the studies involved, such as midazolam, diazepam, dexmedetomidine, etomidate, and propofol; these sedatives are beneficial to reduce PONV and other adverse events. In addition, the dosage of S-ketamine for patient-controlled analgesia was also low post-cesarean delivery (0.5mg/ kg) (12), which may explain the unchanged incidence of postoperative adverse events. We also found that Sketamine not only reduced analgesia scores in the early postoperative period, but also decreased the incidence of hyperalgesia (7), postpartum depression (19), and postoperative sleep disturbance (10), which is in line with a previous studies that the incidence of demoralization was lower in patients who received S-ketamine. Although the use of S-ketamine administration for pain management post-abdominal surgery has surged, the ideal dosage has not been determined. Therefore, more clinical studies are needed to explore the ideal drug dosage of S-ketamine.

Limitations

Our study has some limitations. First, the number of trials included in this study was relatively small, and the overall studies were not of high quality. Second, remarkable heterogeneity was found in the pooled results at each time point post-abdominal surgery might affect the credibility of the results. Third, we did not find any evidence of reduced postoperative complications after the use of S-ketamine in abdominal surgery. Since the observation indexes of postoperative complications in abdominal surgery were not unified among the different studies, this may affect the accuracy of the results. Therefore, large-scale RCTs are needed to investigate the safe and effective dose of S-ketamine in the future.

CONCLUSION

In conclusion, S-ketamine is effective in reducing early postoperative pain in abdominal surgery, and does not increase the incidence of PONV and psychotomimetic adverse events.

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Supplemental material available at www.painphysicianjournal.com

REFERENCES

- Adams HA, Werner C. From the racemate to the eutomer: (S)ketamine. Renaissance of a substance?. [Article in German] Anaesthesist 1997; 46:1026-1042.
- Jelen LA, Young AH, Stone JM. Ketamine: A tale of two enantiomers. J Psychopharmacol 2021; 35:109-123.
- Zanos P, Moaddel R, Morris PJ, et al. Ketamine and ketamine metabolite pharmacology: Insights into therapeutic mechanisms. *Pharmacol Rev* 2018; 70:621-660.
- Schatzberg AF. Mechanisms of action of ketamine and esketamine. Am J Psychiatry 2021; 178:1130.
- Pfenninger EG, Durieux ME, Himmelseher S. Cognitive impairment after small-dose ketamine isomers in comparison to equianalgesic racemic ketamine in human volunteers. Anesthesiology 2002; 96:357-366.
- Bonaventura J, Lam S, Carlton M, et al. Pharmacological and behavioral divergence of ketamine enantiomers: Implications for abuse liability. *Mol Psychiatry* 2021; 26:6704-6722.
- Bornemann-Cimenti H, Wejbora M, Michaeli K, Edler A, Sandner-Kiesling A. The effects of minimaldose versus low-dose S-ketamine on opioid consumption, hyperalgesia, and postoperative delirium: A tripleblinded, randomized, active- and placebo-controlled clinical trial. *Minerva Anestesiol* 2016; 82:1069-1076.
- Massoth C, Schwellenbach J, Saadat-Gilani K, et al. Impact of opioid-free anaesthesia on postoperative nausea, vomiting and pain after gynaecological laparoscopy - A randomised controlled trial. J Clin Anesth 2021; 75:110437.
- 9. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine

for acute postoperative pain in adults: A systematic review and meta-analysis. J Clin Anesth 2021; 68:110071.

- Qiu D, Wang XM, Yang JJ, et al. Effect of intraoperative esketamine infusion on postoperative sleep disturbance after gynecological laparoscopy: A randomized clinical trial. JAMA Netw Open 2022; 5:e2244514.
- Xin N, Yan W, Jin S. Efficacy of analgesic propofol/esketamine and propofol/ fentanyl for painless induced abortion: A randomized clinical trial. *Biomed Res Int* 2022; 2022:5095282.
- Han Y, Li P, Miao M, Tao Y, Kang X, Zhang J. S-ketamine as an adjuvant in patient-controlled intravenous analgesia for preventing postpartum depression: A randomized controlled trial. BMC Anesthesiol 2022; 22:49.
- Hemmerling TM. Pain management in abdominal surgery. Langenbecks Arch Surg 2018; 403:791-803.
- 14. Hughes MJ, Ventham NT, McNally S, Harrison E, Wigmore S. Analgesia after open abdominal surgery in the setting of enhanced recovery surgery: A systematic review and meta-analysis. JAMA Surg 2014; 149:1224-1230.
- Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of delirium and other major complications on outcomes after elective surgery in older adults. JAMA Surg 2015; 150:1134-1140.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021; 372:n71.
- Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014; 14:135.

- Giang HTN, Ahmed AM, Fala RY, et al. Methodological steps used by authors of systematic reviews and meta-analyses of clinical trials: A cross-sectional study. BMC Med Res Methodol 2019; 19:164.
- Argiriadou H, Himmelseher S, Papagiannopoulou P, et al. Improvement of pain treatment after major abdominal surgery by intravenous S+-ketamine. Anesth Analg 2004; 98:1413-1418.
- 20. Snijdelaar DG, Cornelisse HB, Schmid RL, Katz J. A randomised, controlled study of peri-operative low dose s(+)-ketamine in combination with postoperative patient-controlled s(+)ketamine and morphine after radical prostatectomy. Anaesthesia 2004; 59:222-228.
- Miziara LE, Simoni RF, Esteves LO, Cangiani LH, Grillo-Filho GF, Paula AG. Efficacy of continuous S(+)-ketamine infusion for postoperative pain control: A randomized placebo-controlled trial. Anesthesiol Res Pract 2016; 2016;6918327.
- Ithnin FB, Tan DJA, Xu XL, Tan CH, Sultana R, Sng BL. Low-dose S+ ketamine in target-controlled intravenous anaesthesia with remifentanil and propofol for open gynaecological surgery: A randomised controlled trial. *Indian J Anaesth* 2019; 63:126-133.
- Ljungqvist O, de Boer HD, Balfour A, et al. Opportunities and challenges for the next phase of enhanced recovery after surgery: A review. JAMA Surg 2021; 156:775-784.
- 24. Myles PS, Boney O, Botti M, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: Patient comfort. Br J Anaesth 2018; 120:705-711.







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Han 2022 2.35 0.71 122 2.07 0.68 153 42.5% -0.52[0.08,-0.36] Ithini 2019 3.4 1.8 45 3 1.9 44 4.3% 0.40[0.031,051] Massoft 2021 3.1 1 76 3 1.5 76 0.0% 0.40[0.031,051] Ou 2022 2 1.5 92 2.6 0.8 91 17.1% -0.60[0.95,-0.25] Entidelaar 2004 1.2 1 1.3 2 1.4 12 2.9% -0.80[-1.76,0.16] Tetal (95% Cf) 309 334 100.0% -0.48[-0.64,-0.31] Heterospentity Tau? = 0.01; Chr# = 6.45, df = 5 (P = 0.26); P = 22% Test for overall effect Z = 5.71 (P < 0.00001) B Subdy of Subor come Mean SD Total Weight N, Randeen, 95% C1 Gun 2022 2.4 0.8 92 2.6 0.8 91 48.4% -0.20[0.43, 0.03] Gun 2022 2.4 0.8 92 2.6 0.8 91 48.4% -0.20[0.43, 0.03] Gun 2022 2.4 0.8 92 2.6 0.8 91 48.4% -0.20[0.43, 0.03] Gun 2022 2.4 0.8 92 2.6 0.8 91 48.4% -0.20[0.43, 0.03] Tetal (95% Cf) 1.2 9 110 100.0% -0.30[-0.50, 0.11] Heterospentity Tau? = 0.01; Chr# = 1.50, df = 1 (P = 0.26); P = 32%	Bomemann-Cimenti 2016	1.5	0.4	37	2	0.8	19	21.4%	-0.50 [-0.80, -0.20]					
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Snijdelaar 2004 1.2 1 3.2 1.4 1.2 2.9% -0.00[-1.76, 0.16] Tetal (95% Cl) 339 334 100.0% -0.48 [-0.64, -0.31] -0.48 [-0.64, -0.31] Heterogeneity: Tau" = 0.01; Chr# = 6.45, df = 5 (P = 0.26); P = 23% -0.48 [-0.64, -0.31] -0.48 [-0.64, -0.31] Test for overall effect Z = 5.71 (P < 0.00001) Skotamine Centrol Mean Difference Mean Difference Study of Subtroam Mean SD Total (Mean SD Total (Weinfit N. Randem, 95% Cl Mcan Difference Bomemane-Cimenti 2016 2.5 0.4 37 2.9 0.4 1.9 51.6% -0.40 [-0.62, -0.16] Gui 2022 2.4 0.8 9.2 2.6 0.8 9.1 48.4% -0.20 [-0.43, 0.03] Snijdelaar 2004 1.1 1.3 0.5 0.4 1.2 0.0% .60.0 [-0.60, 0.11] Tetal (95% Cl) 12.9 110 100.0% .0.30 [-0.560, 0.01] .0.30 [-0.560, 0.11]	Qiu 2022	2	1.5	92	2.6	0.8	91	17.1%	-0.60[-0.95, -0.25]					
Stotk of Subtroam Stotk of Site Site Site Site Site Site Site Site	Snijdelaar 2004	1.2	1	13	2	1.4	12	2.0%	-0.80 [-1.76, 0.16]					
Heterogeneity: Tau" = 0.01; Ch" = 6.45, df = 5 (P = 0.26); P = 23% Test for overall effect: Z = 5.71 (P < 0.00001) Stork or Sibury: Colspan="2">Mean SD: Total Mean Difference Mean SD: Total Mean SD: Total Weinful: IV, Randem, 95% CI Mean Difference Mean Difference Stork of Sibury: Colspan="2">Mean Difference Mean Difference Mean Difference Mean Difference Bomemann-Cimenti 2016 2.5 0.4 37 2.9 0.4 19 51.6% -0.40.{0.62,-0.16] Mean Difference Bomemann-Cimenti 2016 2.5 0.4 37 2.9 0.4 19 51.6% -0.40.{0.62,-0.16] Mean Difference Bomemann-Cimenti 2016 2.5 0.4 37 2.9 0.4 19 51.6% -0.40.{0.62,-0.16] Mean Difference Bomemann-Cimenti 2016 2.5 0.4 37 2.9 0.4 19 51.6% -0.20.{0.61,0.20] Mean Difference Bomemann-Cimenti 2016 2.5 0.4 12 0.0% -0.20.{0.61,0.20]	Total (95% CB			339			334	100.0%	-0.481-0.64, -0.311	•				
B S-ketamine Centrol Mean Difference Mean Difference Mean Difference Study of Subarcom Mean SD Total Mean SD Total Mean SD Kein SD SD <td< td=""><td>Heterogeneity: Tau^a = 0.01; Test for overall effect Z = 5.</td><td>Ch/#=6. 71 (P < 0</td><td>45, df 00001</td><td>= 5 (P = 1)</td><td>0.26);1</td><td>P# 23</td><td>*</td><td></td><td></td><td>2 -1 0 1 Favours (S-ketamine) Favours (control)</td><td>1</td></td<>	Heterogeneity: Tau ^a = 0.01; Test for overall effect Z = 5.	Ch/#=6. 71 (P < 0	45, df 00001	= 5 (P = 1)	0.26);1	P# 23	*			2 -1 0 1 Favours (S-ketamine) Favours (control)	1			
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Gial 2022 2.4 0.5 92 2.6 0.8 91 48.4% -0.20 [0.4, 0.03] Snijdelaar 2004 1.1 1.2 13 0.5 0.4 12 0.0% 0.60 [0.09, 1.29] Total (95% Cl) 129 110 100.0% -0.30 [-0.50, -0.11] ↓ Intercogenety Tau ² = 0.01; Ch ² = 1.50, df = 1.69 = 0.22; P = 33%	ELOPARO SEAL COROLEMS TOTAL	2.5	0.4	31	2.9	0.4	19	51.6%	-0.40 [-0.67, -0.18]					
Smilleesar 2004 1.1.1.2.1.3.0.5.0.4.1.2.0.0% 0.60 [-0.0%,1.24] Tetal (95% Cl) 129 110 100.0% -0.30 [-0.50, -0.11] ♦ Histerogeneity: Tau [#] = 0.01; Chi [#] = 1.50; df = 1.0 ² = 0.22; i [#] = 33%	Dougenian Content 2010		0.8	92	2.6	0.8	. 91	48.4%	-0.201-0.43, 0.031					
Total (95% Cl) 129 110 100.0% -0.30 [-0.50, -0.11] Historopeneity: Tau [#] = 0.01; Chi [#] = 1.50; df = 1.0 ² = 0.22); i [#] = 33%	Qiu 2022	1.1	3.2	13	0.5	0.4	12	0.0%	0.601-0.04,1.24	100				
Histerogeneity: Tau# = 0.01; Chi# = 1.50; df = 1.02; # = 33%	Qiu 2022 Snijdelaar 2004			1.000			110	100.0%	-0.301-0.50, -0.111	•				
	Oiu 2022 Snijdetaar 2004 Total (95% CI)			129		1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	4		1		-			
Test for overall effect Z = 3 03 (P = 0.002) -4 -2 0 2	Olu 2022 Snijdelaar 2004 Total (95% Cl) Heteropenety: Tau ^e = 0.01;	Chi# = 1	50, df (1.0P	0.225.1	r# 33				4				
Parents (5-wranning Pavents (Control	Olu 2022 Snijdetaar 2004 Total (95% CI) Hateropeneity: Tau* = 0.01; Test for overall effect Z = 3.	Chi# = 1 : 33 (P = 0	50, df	1 (P	0.22);	P # 33				Farmer Kindersterl Farmer Kinder				
	Oiu 2022 Snijdefaar 2004 Tetal (95% CI) Heterogeneity: Tau ⁴ = 0.01; Test for overall effect: Z = 3	Chi# = 1 : 33 (P = 0	50, df 002)	129 1 (P	0.22),	r# 33			2.5	Favours (S-kotamine) Favours (Control)				

Supplemental Table 1. Search strategies

Search terms with no restrictions on study design, outcomes, and language											
PubMed 502	(((((pain) OR (analgesia)) OR (surgery)) OR (postoperative)) OR (opioids)) AND ((S-ketamine) OR (esketamine))										
	#1 TS=((pain) OR (analgesia) OR (surgery) OR (postoperative) OR (opioids))										
Web of Science 299	#2 TS=((S-ketamine) OR (esketamine))										
	#3 #1 AND #2										
	#1 'pain':ab,ti OR 'analgesia':ab,ti OR 'surgery':ab,ti OR 'postoperative':ab,ti OR 'opioids':ab,ti										
EMBASE 364	#2 'S-ketamine':ab,ti OR 'esketamine':ab,ti										
	#3 #1 AND #2										
	#1 (pain):ti,ab,kw OR (analgesia):ti,ab,kw OR (postoperative):ti,ab,kw OR (opioids):ti,ab,kw										
Cochrane Liborary 453	#2 (S-ketamine):ti,ab,kw OR (esketamine):ti,ab,kw										
	#3 #1 AND #2										

		Importance		IMPORTANT		IMPORTANT		IMPORTANT		IMPORTANT		IMPORTANT		IMPORTANT		IMPORTANT
		Certainty		000 DOW		⊕⊕⊕⊖ MODERATE		⊕⊕⊖⊖ Low		⊕⊕⊕⊖ MODERATE		⊕⊕⊕⊖ MODERATE		ФФФФ НІGН		ФФФФ НІСН
		Absolute (95% CI)		SMD -1.12(-1.58, -0.66)		SMD -037(-0.59, -0.15)		SMD 0.05(-0.69, 0.78)		SMD -0.47(-0.67, -0.26)		SMD -0.14(-0.5, 0.21)		17 fewer per 1000 (from 26 fewer to 71 more)		35 fewer per 1000 (from 15 fewer to 108 more)
	Effect	Relative (95% CI)				ı		ı		ı		ı		RR 1.11 (0.75 to 1.65)		RR 1.3 (0.87 to 1.94)
	ıts	Control		367		410		198		122		122		111/518 (21.4%)		37/321 (11.5%)
	No. of patien	S-ketamine		358		415		218		142		142		121/506 (23.9%)		42/293 (14.3%)
		Other considerations		none		none		none		none		none		none		none
		Imprecision		not serious		not serious		not serious		not serious		not serious		no serious		not serious
· Come to an est		Indirectness		not serious		not serious		not serious		not serious		not serious		not serious		not serious
		Inconsistency		serious ^{b.c.d}	gery	serious ^{b.c.d}	gery	serious ^{b.c.d}	er surgery	serious ^{b.c.d}	er surgery	serious ^{b.c.d}		serious ^{b.c.d}	se events	serious ^{b.c.d}
		Risk of bias	fter surgery	not serious ^a	rs after surg	not serious ^a	rs after surg	not serious ^a	24 hours aft	not serious ^a	48 hours aft	not serious ^a	vomiting	not serious ^a	metic advei	not serious ^a
	r assessment	Study design	scores 4 hours a	Randomized trials	scores at 24 hou	Randomized trials	scores at 48 hou	Randomized trials	t pain scores at	Randomized trials	t pain scores at	Randomized trials	tive nausea and	Randomized trials	tive psychotomi	Randomized trials
	Certainty	No. of studies	Rest pain :	9	Rest pain :	7	Rest pain :	4	Movemen	3	Movemen	3	Postoperat	Ν	Postoperat	Ŋ

Supplemental Table 2. GRADE assessment of the overall quality of included studies.

CI: confidence interval; RR: risk ratio a. Performance bias b. Heterogeneity c.Selection bias d.Attrition bia