Pain Physician 2023; 26:327-335 • ISSN 1533-3159

Systematic Review

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

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Disclaimer: M Xie and Y Liang contributed equally to this work. This work was supported by Sichuan Science and Technology Program (No. 2022YFS0106).

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 01-06-2023
Revised manuscript received: 01-23-2023
Accepted for publication: 03-06-2023

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

Pain Physician 2023: 26:327-335

S-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 meta-analysis 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 meta-analysis 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% CIs, while the continuous variables were described in forms of mean difference (MD) and 95% CIs. Cochran's Q test and Higgins' I^2 statistical test were used to assess the statistical heterogeneity of the pooled results. Heterogeneity is defined as no, low, moderate, and high when I^2 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 post-abdominal surgery were significantly lower in the S-ketamine group (standardized mean difference [SMD] = -1.12; 95% CI, -1.58 to -0.66; $P < 0.00001$; $I^2 = 91\%$; SMD = -0.37; 95% CI, -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% CI,-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; $P =$

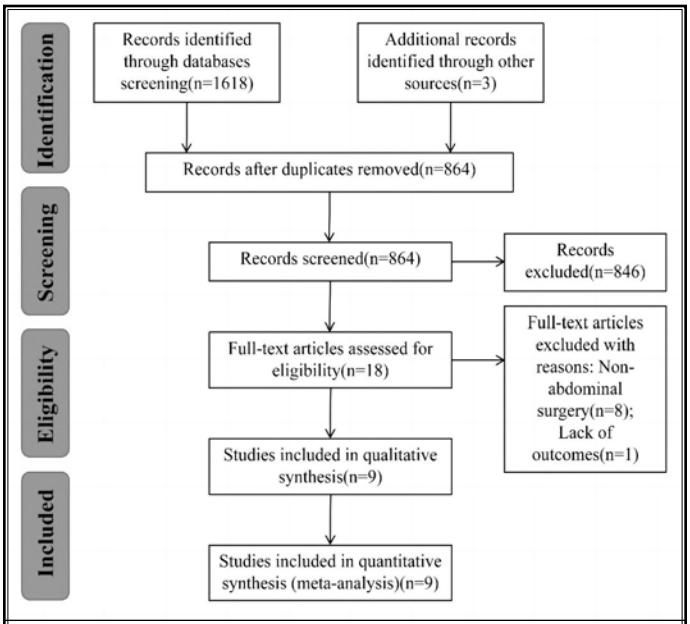

Fig. 1. *Study selection flow diagram.*

Table 1. *Characteristics of the included studies*.

Study	Country	Sample Size		Age (y)		Interventional strategy
		S-ketamine	Control	S-ketamine	Control	
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

Study	Control	Anesthesia maintenance	Postoperative analgesic	Type of surgery	Duration of anesthesia (min)		Duration of surgery (min)	
					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 ± 37.65 134.0 ± 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; I^2 = 19%; RR = 1.3; 95% CI, 0.87 to 1.94; *P* = 0.2; I^2 = 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 S-ketamine 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% CI, -0.81 to -0.24; *P* = 0.0003, I^2 = 0%) compared with the intraoperative use group (SMD = -0.18; 95% CI, -0.59 to 0.23; *P* = 0.4; I^2 = 69%). No significant difference of the pain at rest scores at 48 hours post-abdominal surgery was observed between the 2 groups (Fig. 6). A subgroup analysis of pain with movement scores was not conducted because the number of studies was too small for reliable estimation.

Sensitivity Analysis

The heterogeneity of the pain at rest score at 24 hours post-abdominal 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% CI, -0.5 to -0.11; *P* = 0.002; I^2 = 33%), respectively (Fig. S4).

Discussion

In the present study, we demonstrate

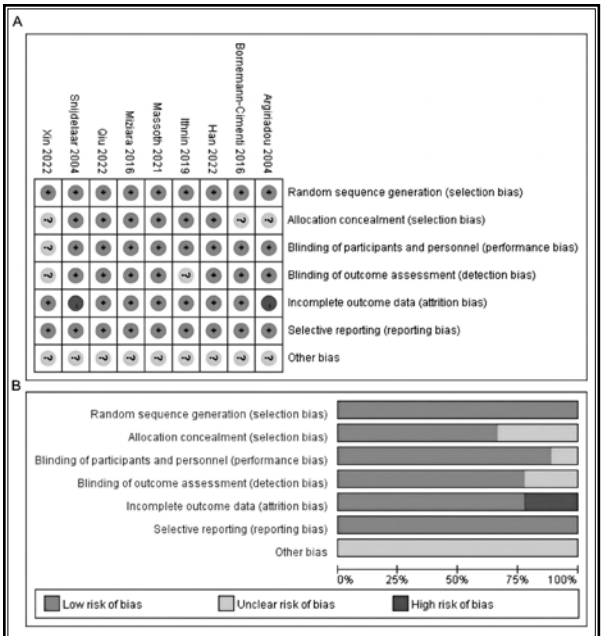

Fig. 2. *Risk of bias. A) A summary of the risks of bias for each study; B) The distribution of each risk of bias across studies. Green represents a low risk of bias, yellow unclear bias, and red a high risk of bias.*

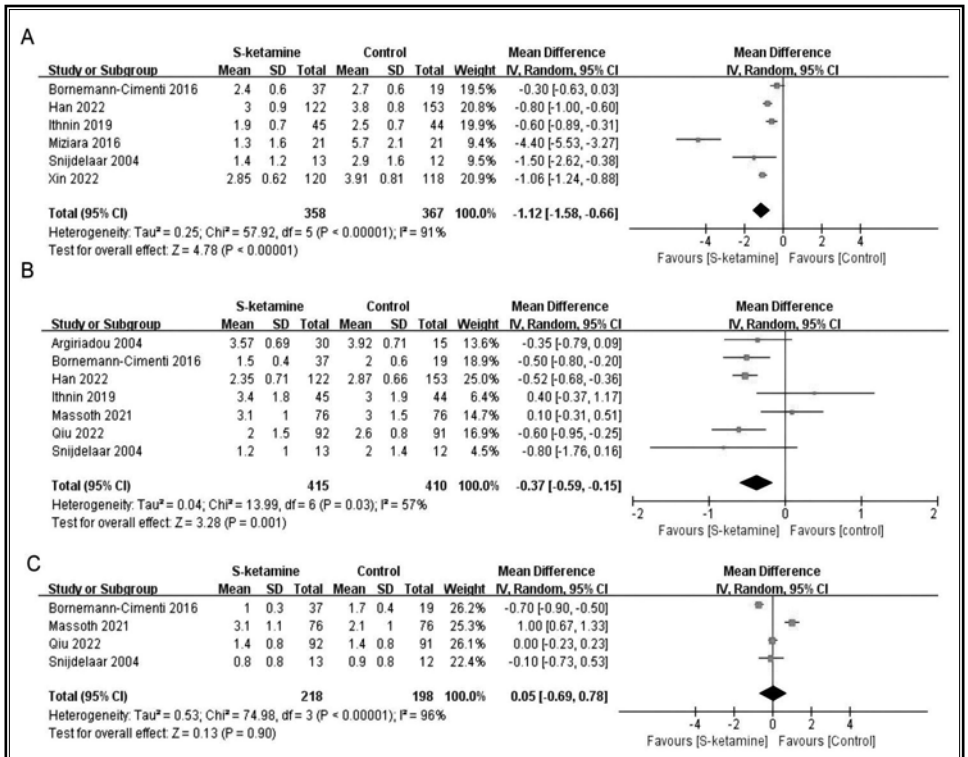

Fig. 3. *Forest plot of postoperative pain scores in patients at rest after abdominal surgery. A. 4 hours postsurgery; B. 24 hours postsurgery; C. 48 hours postsurgery.*

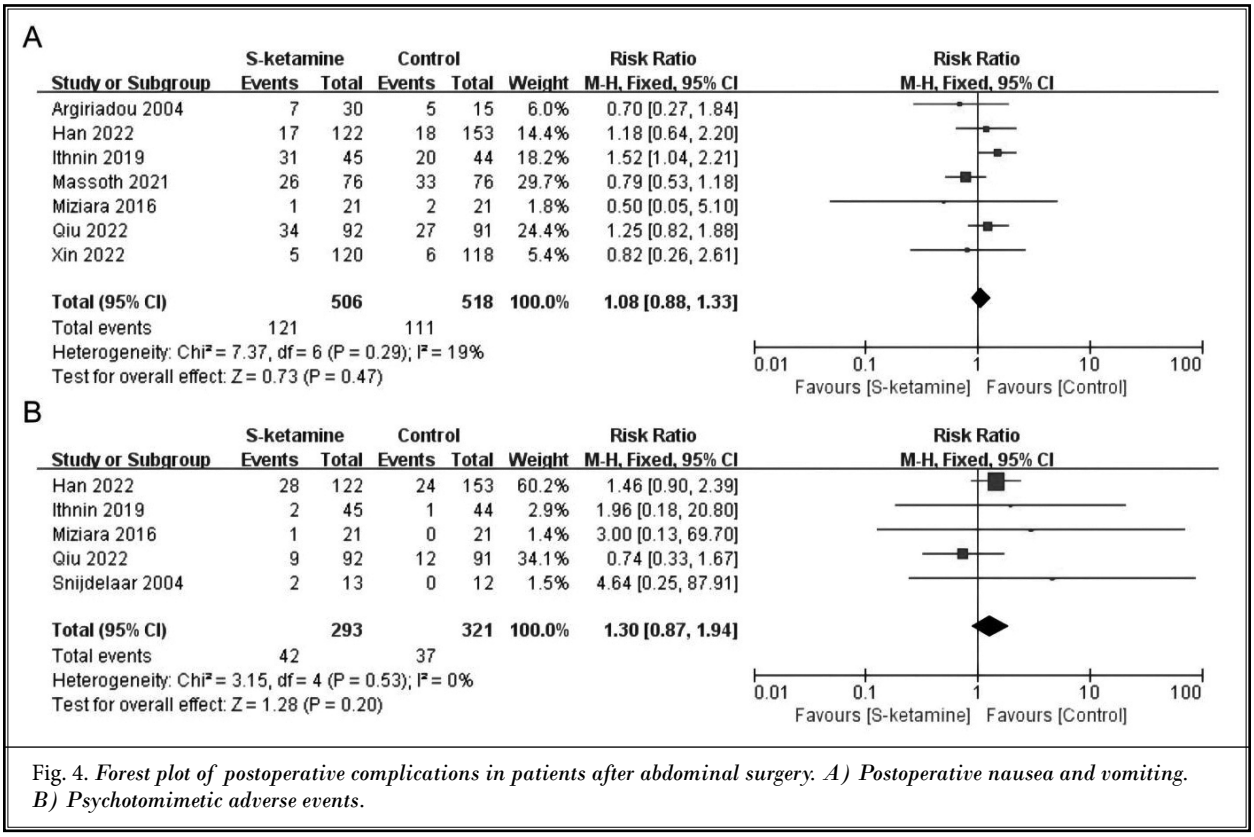

Fig. 4. *Forest plot of postoperative complications in patients after abdominal surgery. A) Postoperative nausea and vomiting. B) Psychotomimetic adverse events.*

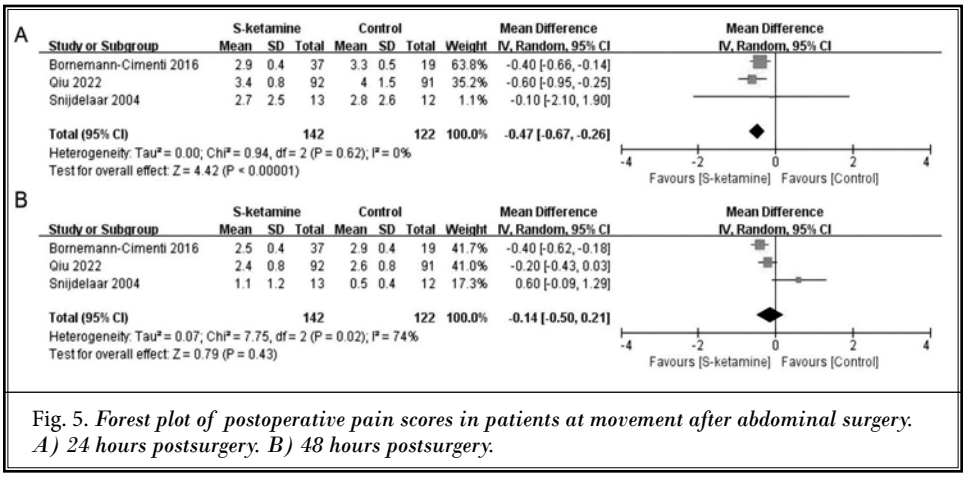

Fig. 5. *Forest plot of postoperative pain scores in patients at movement after abdominal surgery. A) 24 hours postsurgery. B) 48 hours postsurgery.*

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 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 meta-analysis 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 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

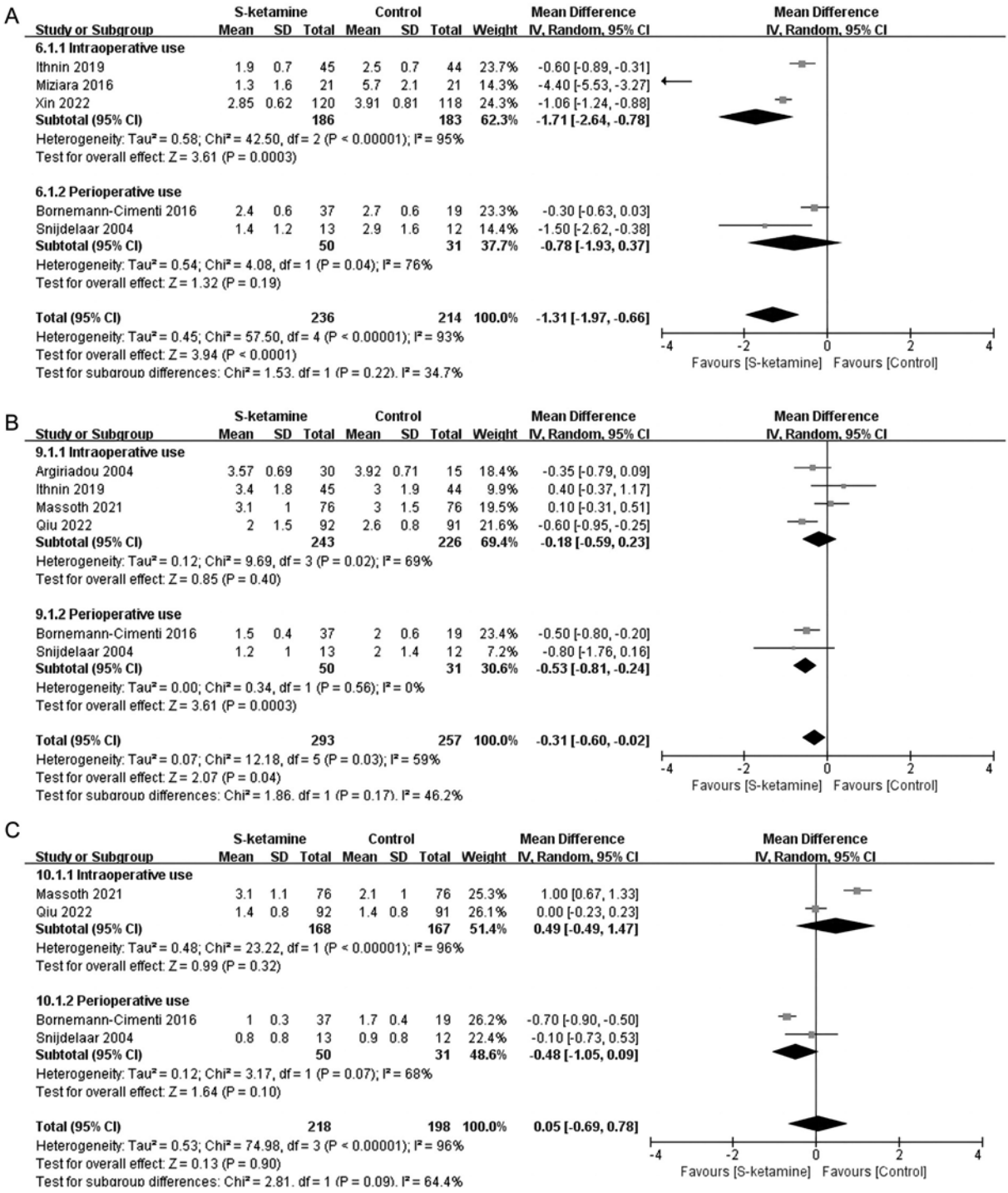

Fig. 6. *Subgroup analysis for postoperative pain scores in patients at rest by administration time. A) 4 hours postsurgery. B) 24 hours postsurgery. C) 48 hours postsurgery.*

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 post-abdominal 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 S-ketamine 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.

Acknowledgments

The authors gratefully acknowledge Fei Peng for his help with the acquisition of data.

Supplemental material available at www.painphysicianjournal.com

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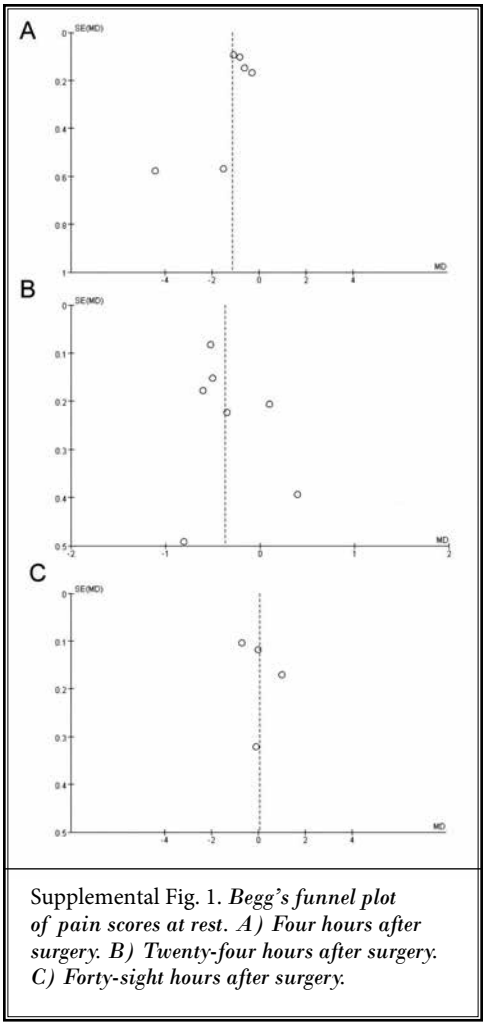
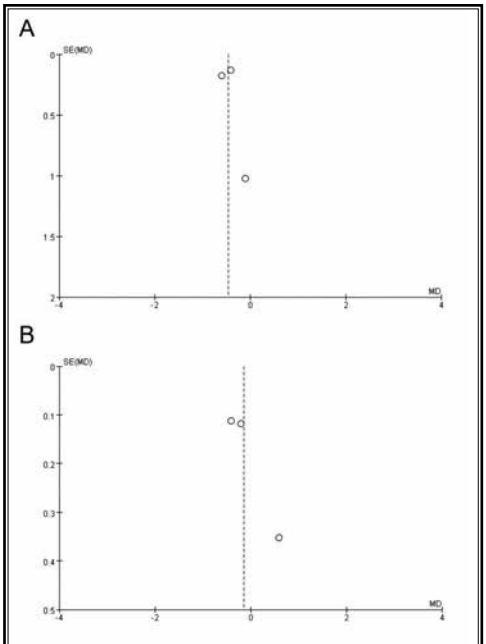
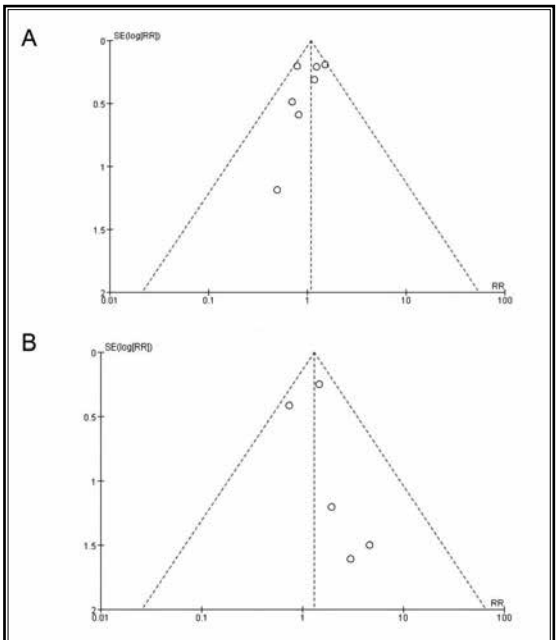


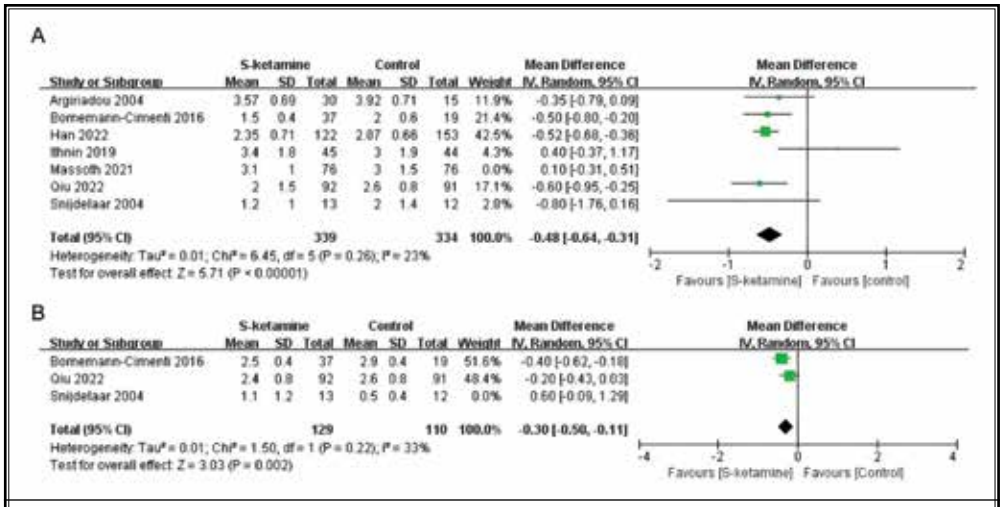
Supplemental Fig. 1. ***Begg's funnel plot of pain scores at rest. A) Four hours after surgery. B) Twenty-four hours after surgery. C) Forty-sight hours after surgery.***



Supplemental Fig. 2. ***Begg's funnel plot of pain scores at movement. A) Twenty-four hours after surgery. B) Forty-sight hours after surgery.***



Supplemental Fig. 3. ***Begg's funnel plot of postoperative complications. A) Postoperative nausea and vomiting. B) Psychotomimetic adverse events.***



Supplemental Fig. 4. *Sensitivity analysis for postoperative pain scores by excluding specific studies. A) Resting pain scores at 24 hours after surgery. B) Movement pain scores at 48 hours after surgery.*

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))
Web of Science 299	#1 TS=((pain) OR (analgesia) OR (surgery) OR (postoperative) OR (opioids))
	#2 TS=((S-ketamine) OR (esketamine))
	#3 #1 AND #2
EMBASE 364	#1 'pain':ab,ti OR 'analgesia':ab,ti OR 'surgery':ab,ti OR 'postoperative':ab,ti OR 'opioids':ab,ti
	#2 'S-ketamine':ab,ti OR 'esketamine':ab,ti
	#3 #1 AND #2
Cochrane Liborary 453	#1 (pain):ti,ab,kw OR (analgesia):ti,ab,kw OR (postoperative):ti,ab,kw OR (opioids):ti,ab,kw
	#2 (S-ketamine):ti,ab,kw OR (esketamine):ti,ab,kw
	#3 #1 AND #2

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

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**S-ketamine**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Rest pain scores 4 hours after surgery												
6	Randomized trials	not serious[a]	serious[b,c,d]	not serious	not serious	none	358	367	-	SMD -1.12(-1.58, -0.66)	⊕⊕◯◯ LOW	IMPORTANT
Rest pain scores at 24 hours after surgery												
7	Randomized trials	not serious[a]	serious[b,c,d]	not serious	not serious	none	415	410	-	SMD -037(-0.59, -0.15)	⊕⊕⊕◯ MODERATE	IMPORTANT
Rest pain scores at 48 hours after surgery												
4	Randomized trials	not serious[a]	serious[b,c,d]	not serious	not serious	none	218	198	-	SMD 0.05(-0.69, 0.78)	⊕⊕◯◯ LOW	IMPORTANT
Movement pain scores at 24 hours after surgery												
3	Randomized trials	not serious[a]	serious[b,c,d]	not serious	not serious	none	142	122	-	SMD -0.47(-0.67, -0.26)	⊕⊕⊕◯ MODERATE	IMPORTANT
Movement pain scores at 48 hours after surgery												
3	Randomized trials	not serious[a]	serious[b,c,d]	not serious	not serious	none	142	122	-	SMD -0.14(-0.5, 0.21)	⊕⊕⊕◯ MODERATE	IMPORTANT
Postoperative nausea and vomiting												
7	Randomized trials	not serious[a]	serious[b,c,d]	not serious	no serious	none	121/506 (23.9%)	111/518 (21.4%)	RR 1.11 (0.75 to 1.65)	17 fewer per 1000 (from 26 fewer to 71 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Postoperative psychotomimetic adverse events												
5	Randomized trials	not serious[a]	serious[b,c,d]	not serious	not serious	none	42/293 (14.3%)	37/321 (11.5%)	RR 1.3 (0.87 to 1.94)	35 fewer per 1000 (from 15 fewer to 108 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

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