

The efficacy of ketamine supplementation on pain management for knee arthroscopy

A meta-analysis of randomized controlled trials

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Abstract

Introduction: The efficacy of ketamine supplementation on pain management for knee arthroscopy remains controversial. We conduct a systematic review and meta-analysis to explore the influence of ketamine supplementation for knee arthroscopy.

Methods: We search PubMed, EMBASE, Web of science, EBSCO, and Cochrane library databases through October 2018 for randomized controlled trials (RCTs) assessing the effect of ketamine supplementation on pain control for knee arthroscopy. This meta-analysis is performed using the random-effect model.

Results: Seven RCTs involving 300 patients are included in the meta-analysis. Overall, compared with control group for knee arthroscopy, ketamine supplementation reveals favorable impact on pain scores (mean difference [MD]=−2.95; 95% confidence interval [CI]=−3.36 to −2.54; $P < .00001$), analgesic consumption (standard mean difference [Std. MD]=−1.03; 95% CI=−1.70 to −0.36; $P = .002$), time to first analgesic requirement (Std. MD= 1.21; 95% CI=0.45–1.96; $P = .002$) and malondialdehyde (Std. MD=−0.63; 95% CI=−1.05 to 3.10; $P = -.20$), and shows no increase in nausea and vomiting (RR= 1.87; 95% CI=0.65–3.10; $P = .003$).

Conclusions: Ketamine supplementation benefits to pain management and may reduce ischemia reperfusion injury in patients with knee arthroscopy.

Abbreviations: CI = confidence interval, RCTs = randomized controlled trials, SMD = standard mean difference.

Keywords: ketamine supplementation, knee arthroscopy, meta-analysis, pain management, randomized controlled trials

1. Introduction

Postoperative pain widely occurs in patients undergoing knee arthroscopy, and has become one of the main causes of delayed discharge and rehabilitation.^[1–3] Many methods have been developed to prevent or treat pain following arthroscopic knee surgery, and they include systemic opioid and non-opioid analgesics, central and peripheral nerve blocks, preemptive analgesia, and intraarticular drug administration.^[4–6] The duration of analgesia is typically short, and the use of combined drugs has increased progressively and holds important promise for pain relief after knee arthroscopy.^[7,8]

Different drugs can act in synergy and the side effects of a single drug with high dose can be reduced or avoided.^[9,10] For instance, dexamethasone added to ropivacaine is found to increase the duration of analgesia of an interscalene block from an average of 11.8 to 22.2 hours,^[11] and this prolonged analgesia of perineural dexamethasone may be caused by the direct action on the nerve or through systemic absorption.^[12,13] Ketamine is known as an analgesic and anesthetic agent which has peripheral analgesic effects on pain and hyperalgesia with a variable duration.^[4] Many studies have confirmed the efficacy of ketamine and levobupivacaine combination for pain relief in arthroscopic surgery.^[5,6]

However, the efficacy of ketamine supplementation for knee arthroscopy has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting.^[14–17] With accumulating evidence, we therefore perform a systematic review and meta-analysis of RCTs to compare the efficacy of ketamine supplementation versus placebo for knee arthroscopy.

2. Materials and methods

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).^[18]

2.1. Search strategy and study selection

Two investigators have independently searched the following databases (inception to October 2018): PubMed, EMBASE, Web of science, EBSCO, and Cochrane library databases. The

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LP and YS have contributed equally.

TM and HX have contributed equally.

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electronic search strategy is conducted using the following keywords ketamine, and knee arthroscopy. We also check the reference lists of the screened full-text studies to identify other potentially eligible trials.

The inclusive selection criteria are as follows: population: patients undergoing knee arthroscopy; intervention: ketamine supplementation; comparison: placebo; study design: RCT.

2.2. Data extraction and outcome measures

We have extracted the following information: author, number of patients, age, women, weight or body mass index, American Society of Anesthesiologists (ASA), and detail methods in each group etc. Data have been extracted independently by 2 investigators, and discrepancies are resolved by consensus. We also contact the corresponding author to obtain the data when necessary.

The primary outcomes are pain scores within 2 hours. Secondary outcomes include analgesic consumption, time to first analgesic requirement, malondialdehyde, nausea, and vomiting.

2.3. Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale.^[19] There are 3 items for Jadad scale: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points). The score of Jadad Scale

varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3 , the study is thought to be of high quality.^[20]

2.4. Statistical analysis

We estimate the standard mean difference (Std. MD) or mean difference (MD) with 95% confidence interval (CI) for continuous outcomes (pain scores within 2 hours, analgesic consumption, time to first analgesic requirement, and malondialdehyde) risk ratios (RRs) with 95% CIs for dichotomous outcomes (nausea and vomiting). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity.^[21] Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting 1 study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results

3.1. Literature search, study characteristics, and quality assessment

A detailed flowchart of the search and selection results is shown in Fig. 1. Five hundred twenty one potentially relevant articles are

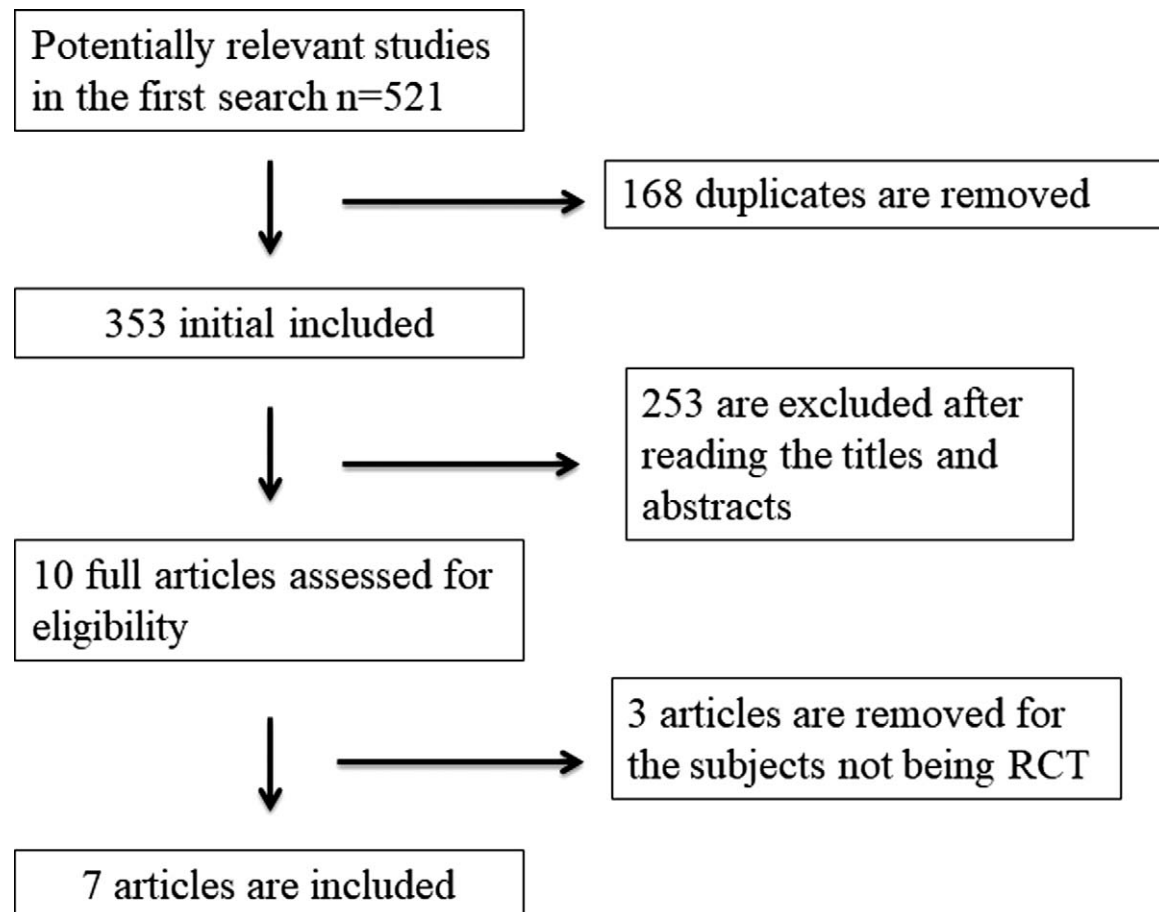


Figure 1. Flow diagram of study searching and selection process.

Table 1
Characteristics of included studies.

No.	Author	Ketamine group				Control group				Jada scores			
		Number	Age, y	Female (n)	Body mass index (kg/m ²) or weight (kg)	ASA I/II (n)	Methods	Number	Age (years)		Female (n)	Body mass index (kg/m ²) or weight (kg)	ASA I/II (n)
1	Isik 2015	20	38.6±11.5	11	26.6±4.1	-	1.0mg/kg of intraarticular ketamine in 20 mL of normal saline	20	34.3±13.9	8	24.7±4.7	-	20mL of intraarticular normal saline
2	Gogus 2014	30	44.6±11.5	14	79.6±8.7	15/15	Intravenous 0.5 mg/kg/h of ketamine and 2mg/kg/h of propofol combination	30	39.7±9.3	15	81.4±14.9	16/14	The equivalent volume of saline
3	Ayoglu 2010	20	40.9±2.9	8	78.8±2.7	-	Intraarticular 50mg tramadol with 0.5mg/kg ketamine	20	41.5±2.9	12	70.4±2.0	-	Intraarticular 50mg tramadol
4	Çalgı 2009	20	16-65	9	55-97	-	Intravenous ketamine 0.15 mg/kg	20	31-60	10	56-98	-	Intravenous saline
5	Sarıcaoglu 2005	15	31±8	6	69±14	-	Intravenous administration of 0.01 mg/kg midazolam, a continuous infusion of ketamine (0.5 mg/kg/h)	15	30±7	5	71±11	-	Volume-equivalent placebo
6	Batra 2005	20	35±4	8	72±4	-	A combination of 1.0mg/kg ketamine and 0.25% bupivacaine to a total volume of 20 mL by intra-articular route	20	44±3	4	68±3	-	Intra-articular 20mL 0.25% bupivacaine
7	Menigaux 2001	25	37±9	8	76±13	-	intravenous 0.15 mg/kg ketamine just after the induction of anesthesia	25	36±12	9	73±14	-	Placebo

ASA = American Society of Anesthesiologists.

identified initially. Finally, 7 RCTs that meet our inclusion criteria are included in the meta-analysis.^[4,14-17,22,23]

The baseline characteristics of the 7 eligible RCTs in the meta-analysis are summarized in Table 1. The 7 studies are published between 2001 and 2015, and sample sizes range from 40 to 60 with a total of 300. Ketamine is administered by 0.5 to 1.0 mg/kg of intraarticular injection, or 0.01 to 0.15 mg/kg of intravenous infusion. It is also used in combination with propofol,^[15] tramadol,^[16] midazolam,^[22] or bupivacaine.^[4]

Among the 7 studies included here, 2 studies report pain scores within 2 hours,^[16,22] 3 studies report analgesic consumption,^[4,16,17] 3 studies report time to first analgesic requirement,^[4,17,22] 2 studies report malondialdehyde,^[15,22] and 2 studies report nausea and vomiting.^[14,16] Jadad scores of the 7 included studies vary from 3 to 5, and all 7 studies are considered to be high-quality ones according to quality assessment.

3.2. Primary outcome: pain scores within 2 hours

This outcome data is analyzed with the random-effects model, and compared with control group for knee arthroscopy, ketamine supplementation exerts positive influence on pain scores within 2 hours (MD=-2.95; 95% CI=-3.36 to -2.54; P<.00001), with no heterogeneity among the studies (I²=0%, heterogeneity P=.48) (Fig. 2).

3.3. Sensitivity analysis

No heterogeneity is observed among the included studies for pain scores within 2 hours, and thus we do not perform sensitivity analysis via omitting one study in turn to detect the heterogeneity.

3.4. Secondary outcomes

In comparison with control group for knee arthroscopy, ketamine supplementation is associated with significantly reduced analgesic consumption (Std. MD=-1.03; 95% CI=-1.70 to -0.36; P=.002; Fig. 3), increased time to first analgesic requirement (Std. MD=1.21; 95% CI=0.45-1.96; P=.002; Fig. 4), and decreased malondialdehyde (Std. MD=-0.63; 95% CI=-1.05 to 3.10; P=-.20; Fig. 5). The incidence of nausea and vomiting shows no statistical difference between 2 groups (RR=1.87; 95% CI=0.65-3.10; P=.003; Fig. 6).

4. Discussion

Many factors can cause postoperative pain after arthroscopic surgery, and pain intensity is determined by the operation procedures.^[24,25] For instance, arthroscopic anterior cruciate ligament reconstruction and meniscus repair result in postoperative pain at different levels.^[6] The relief in postoperative pain is crucial for early postoperative rehabilitation and prevention of potential complications. Many anesthetic agents (e.g., opioids, ketamine, and clonidine) have been utilized alone or as adjuvant agents for pain control after arthroscopic knee surgery.^[26,27] When intraarticular drugs are applied alone, their time of effect is short, and increased utilization of drug combinations may amplify the analgesic effect.^[4,28]

Ketamine acts through interacting with many receptors such as N-methyl-D-aspartate (NMDAr), serotonergic, and adrenergic receptors, which exhibit important roles in analgesia. NMDAr is located in the peripheral and somatic pain pathways, and it has an

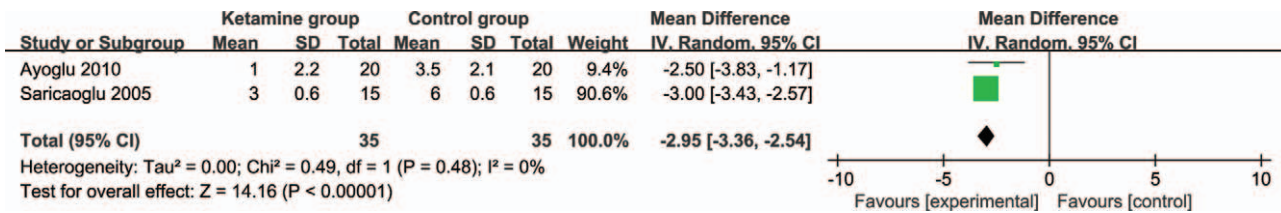


Figure 2. Forest plot for the meta-analysis of pain scores within 2 hours.

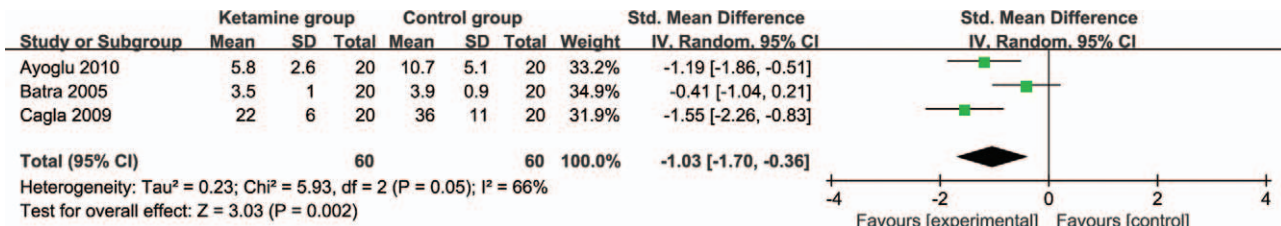


Figure 3. Forest plot for the meta-analysis of analgesic consumption.

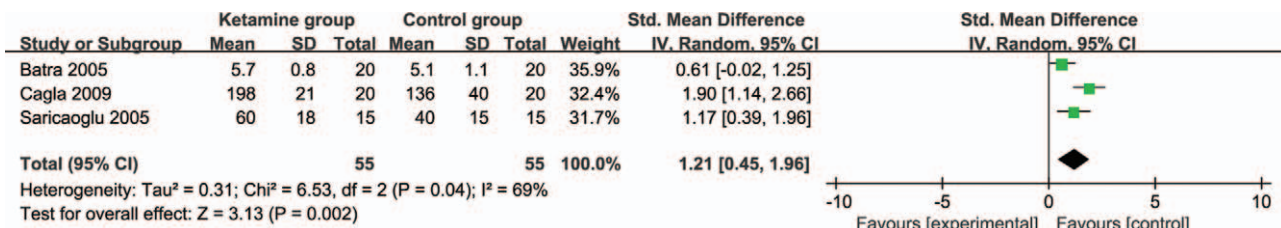


Figure 4. Forest plot for the meta-analysis of time to first analgesic requirement.

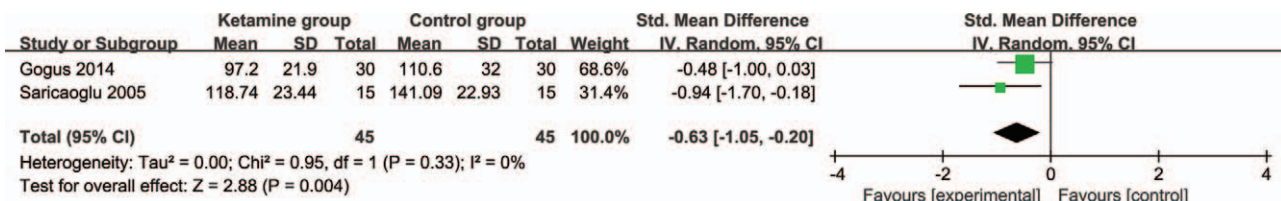


Figure 5. Forest plot for the meta-analysis of malondialdehyde.

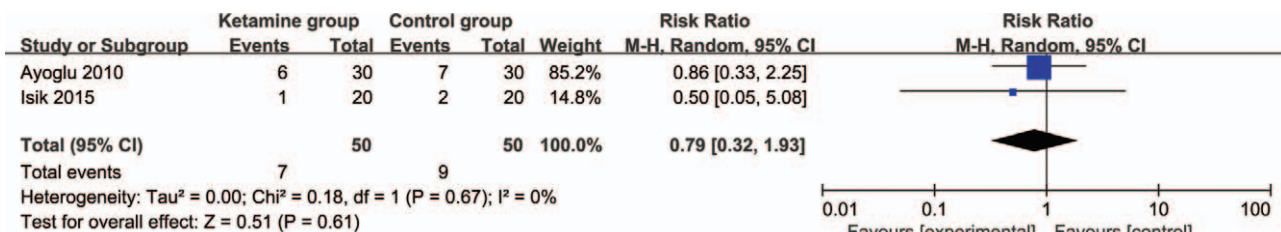


Figure 6. Forest plot for the meta-analysis of nausea and vomiting.

important role in nociception.^[29] Ketamine has been applied either alone or as an intraarticular adjuvant.^[5,16] Several studies have confirmed the efficacy of intraarticular ketamine in postoperative pain treatment after arthroscopic knee surgery,^[4,30] whereas the conflicting results are observed in another study.^[31] Our meta-analysis concludes that ketamine supplementation is associated with remarkably reduced pain scores within 2 hours, analgesic consumption, and prolonged time to first analgesic requirement for knee arthroscopy.

After the tourniquet is released, excessive formation of reactive oxygen species leads to peroxidation of membrane lipids during ischemia reperfusion injury, which subsequently stimulates oxidation of the polyunsaturated fatty acids, destroying membrane structures and producing toxic metabolites such as malondialdehyde.^[32–34] Malondialdehyde in ketamine supplementation group is substantially lower than that in control group for knee arthroscopy based on the results of our meta-analysis, suggesting the potential of ketamine supplementation group in alleviating

ischemia reperfusion injury. There is no significant difference of nausea and vomiting between 2 groups. Regarding the sensitivity analysis, although there is no significant heterogeneity, several factors may have some effect on the pooling results. They mainly include different doses, routes and combination of ketamine supplementation, as well as various operation procedures etc.

This meta-analysis has several potential limitations. Firstly, our analysis is based on 7 RCTs, and all of them have a relatively small sample size ($n < 100$). These may lead to overestimation of the treatment effect in smaller trials. More RCTs with large sample size should be conducted to explore this issue. Next, various doses, routes, and combination of ketamine supplementation are included in this meta-analysis, which may have some impact on the pooling results. Finally, different operation procedures are performed for knee arthroscopy, and may also affect the pooled results.

5. Conclusions

Ketamine supplementation exhibits additional benefits for pain control in patients with knee arthroscopy.

Author contributions

Conceptualization: Linlin Pan, Teng Ma.

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References

- Chen X, Mou X, He Z, et al. The effect of midazolam on pain control after knee arthroscopy: a systematic review and meta-analysis. *J Orthop Surg Res* 2017;12:179.
- Hoofwijk DM, Fiddelers AA, Emans PJ, et al. Prevalence and predictive factors of chronic postsurgical pain and global surgical recovery 1 year after outpatient knee arthroscopy: a prospective cohort study. *Medicine (Baltimore)* 2015;94:e2017.
- Tepolt FA, Bido J, Burgess S, et al. Opioid overprescription after knee arthroscopy and related surgery in adolescents and young adults. *Arthroscopy* 2018;34:3236–43.
- Batra YK, Mahajan R, Bangalia SK, et al. Bupivacaine/ketamine is superior to intra-articular ketamine analgesia following arthroscopic knee surgery. *Can J Anaesth* 2005;52:832–6.
- Dal D, Tetik O, Altunkaya H, et al. The efficacy of intra-articular ketamine for postoperative analgesia in outpatient arthroscopic surgery. *Arthroscopy* 2004;20:300–5.
- Koltka K, Koknel-Talu G, Asik M, et al. Comparison of efficacy of intraarticular application of magnesium, levobupivacaine and lornoxicam with placebo in arthroscopic surgery. *Knee Surg Sports Traumatol Arthrosc* 2011;19:1884–9.
- Ng HP, Nordstrom U, Axelsson K, et al. Efficacy of intra-articular bupivacaine, ropivacaine, or a combination of ropivacaine, morphine, and ketorolac on postoperative pain relief after ambulatory arthroscopic knee surgery: a randomized double-blind study. *Reg Anesth Pain Med* 2006;31:26–33.
- Talu GK, Ozyalcin S, Koltka K, et al. Comparison of efficacy of intraarticular application of tenoxicam, bupivacaine and tenoxicam: bupivacaine combination in arthroscopic knee surgery. *Knee Surg Sports Traumatol Arthrosc* 2002;10:355–60.
- Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol* 2009;22:588–93.
- Izdes S, Orhun S, Turanlı S, et al. The effects of preoperative inflammation on the analgesic efficacy of intraarticular piroxicam for outpatient knee arthroscopy. *Anesth Analg* 2003;97:1016–9.
- Cummings KC3rd, Napierkowski DE, Parra-Sanchez I, et al. Effect of dexamethasone on the duration of interscalene nerve blocks with ropivacaine or bupivacaine. *Br J Anaesth* 2011;107:446–53.
- Tandoc MN, Fan L, Kolesnikov S, et al. Adjuvant dexamethasone with bupivacaine prolongs the duration of interscalene block: a prospective randomized trial. *J Anesth* 2011;25:704–9.
- Kim YJ, Lee GY, Kim DY, et al. Dexamethasone added to levobupivacaine improves postoperative analgesia in ultrasound guided interscalene brachial plexus blockade for arthroscopic shoulder surgery. *Korean J Anesthesiol* 2012;62:130–4.
- Isik C, Demirhan A, Yetis T, et al. Efficacy of intraarticular application of ketamine or ketamine-levobupivacaine combination on post-operative pain after arthroscopic meniscectomy. *Knee Surg Sports Traumatol Arthrosc* 2015;23:2721–6.
- Gogus N, Akan B, Bayrakci S, et al. The effects of a small-dose ketamine-propofol combination on tourniquet-induced ischemia-reperfusion injury during arthroscopic knee surgery. *J Clin Anesth* 2014;26:46–51.
- Ayoglu H, Altunkaya H, Bayar A, et al. The effect of intraarticular combinations of tramadol and ropivacaine with ketamine on postoperative pain after arthroscopic meniscectomy. *Arch Orthop Trauma Surg* 2010;130:307–12.
- Cagla Ozbakis Akkurt B, Inanoglu K, Kalaci A, et al. Effects of intravenous small dose ketamine and midazolam on postoperative pain following knee arthroscopy. *Pain Pract* 2009;9:289–95.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996;17:1–2.
- Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med* 2001;135:982–9.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
- Saricaoglu F, Dal D, Salman AE, et al. Ketamine sedation during spinal anesthesia for arthroscopic knee surgery reduced the ischemia-reperfusion injury markers. *Anesth Analg* 2005;101:904–9.
- Menigaux C, Guignard B, Fletcher D, et al. Intraoperative small-dose ketamine enhances analgesia after outpatient knee arthroscopy. *Anesth Analg* 2001;93:606–12.
- Uribe AA, Arbona FL, Flanigan DC, et al. Comparing the efficacy of IV Ibuprofen and Ketorolac in the management of postoperative pain following arthroscopic knee surgery. A randomized double-blind active comparator Pilot Study. *Front Surg* 2018;5:59.
- Shen D, Chen M, Chen K, et al. Efficacy of hyaluronic acid after knee arthroscopy: a systematic review and meta-analysis. *J Rehabil Med* 2018;50:860–5.
- Ersan O, Akkaya T, Arik E, et al. Intra-articular levobupivacaine, lornoxicam and morphine analgesia after knee arthroscopy: a randomized, controlled trial. *Acta Orthop Traumatol Turc* 2012;46:411–5.
- Jacobson E, Assareh H, Cannerfelt R, et al. The postoperative analgesic effects of intra-articular levobupivacaine in elective day-case arthroscopy of the knee: a prospective, randomized, double-blind clinical study. *Knee Surg Sports Traumatol Arthrosc* 2006;14:120–4.
- White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. *Anesth Analg* 2005;101:55–22.
- Petrenko AB, Yamakura T, Baba H, et al. The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review. *Anesth Analg* 2003;97:1108–16.
- Borner M, Burkle H, Trojan S, et al. [Intra-articular ketamine after arthroscopic knee surgery. Optimisation of postoperative analgesia]. *Der Anaesthetist* 2007;56:1120–7.
- Huang GS, Yeh CC, Kong SS, et al. Intra-articular ketamine for pain control following arthroscopic knee surgery. *Acta Anaesthesiol Sin* 2000;38:131–6.
- Cheng YJ, Chien CT, Chen CF. Oxidative stress in bilateral total knee replacement, under ischaemic tourniquet. *J Bone Joint Surg Br* 2003;85:679–82.
- Cheng YJ, Wang YP, Chien CT, et al. Small-dose propofol sedation attenuates the formation of reactive oxygen species in tourniquet-induced ischemia-reperfusion injury under spinal anesthesia. *Anesth Analg* 2002;94:1617–20.
- Lee JY, Kim CJ, Chung MY. Effect of high-dose vitamin C on oxygen free radical production and myocardial enzyme after tourniquet ischaemia-reperfusion injury during bilateral total knee replacement. *J Int Med Res* 2010;38:1519–29.