

Ketamine Supplementation To Bupivacaine For Knee Arthroscopy: A Meta-Analysis of Randomized Controlled Trials

Chunhong Li

Hainan Medical University

Zhibo Xiao

Hainan Medical University

Liuli Chen

Hainan Medical University

Songli Pan (✉ ed7713@163.com)

Hainan Medical University

Research Article

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Abstract

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

Methods: We have searched PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases through July 2021 for randomized controlled trials (RCTs) assessing the effect of ketamine supplementation to bupivacaine on pain control of knee arthroscopy. This meta-analysis is performed using the random-effect model.

Results: Four RCTs are included in the meta-analysis. Overall, compared with control group for knee arthroscopy, ketamine supplementation remarkably decreases pain scores at 30 min (SMD=-0.98; 95% CI=-1.42 to -0.55; P<0.00001) and number of additional analgesics (OR=0.27; 95% CI=0.10 to 0.71; P=0.008), but reveals no significant impact on pain scores at 1 h (SMD=-1.34; 95% CI=-3.42 to 0.73; P=0.20), pain scores at 6 h (SMD=-0.33; 95% CI=-1.39 to 0.72; P=0.53), time of first analgesic requirement (SMD=1.27; 95% CI=-0.95 to 3.49; P=0.26) or additional analgesic consumption (SMD=-2.25; 95% CI=-5.89 to 1.40; P=0.23).

Conclusions: Ketamine supplementation may improve the pain control when in combination with bupivacaine for knee arthroscopy.

Introduction

Arthroscopic knee surgery has been widely used in orthopedic surgeries [1–4]. Postoperative pain of knee arthroscopy commonly occurs due to stimulating the bare nerve endpoints and afferent nociceptors, releasing inflammatory mediators such as bradykinin, serotonin and histamine from injured cells [5, 6]. Insufficient pain control may result in prolonged hospital stay and delayed discharge [7–9]. Various analgesia methods have been developed to target the routes of nerves and various neurotransmitters to inhibit hyperalgesia and nociception, which may improve inflammatory and neurogenic conditions [10, 11].

Ketamine shows important analgesic effect in systemic and peripheral use through interacting with a large number of receptors such as opioid, muscarinic, and N-methyl-D-aspartate (NMDA) receptors, and NMDA receptors display a significant role in peripheral somatic and visceral pain pathways [12]. In instance, NMDA receptors exist in the knee joint of the rats, and intraarticular administration of ketamine provides adequate analgesia for arthritic joints [13]. Bupivacaine has been widely used for analgesia, and addition of ketamine to bupivacaine for wound infiltration is documented to prolong the analgesic duration and increase the pain threshold [14].

The addition of ketamine to bupivacaine for the pain management of knee arthroscopy has not been well established, and several studies reported the conflicting results [15–17]. With accumulating evidence, we therefore perform a systematic review and meta-analysis of RCTs to explore the efficacy and safety of ketamine supplementation to bupivacaine in patients with knee arthroscopy.

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, 19].

Search strategy and study selection

Two investigators have independently searched the following databases (inception to July 2021): PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases. The electronic search strategy is conducted using the following keywords: ketamine, bupivacaine 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: (i) study design is RCT; (ii) population are patients who undergo knee arthroscopy; (iii) intervention treatments are ketamine plus bupivacaine versus bupivacaine.

Data extraction and outcome measures

We have extracted the following information: author, number of patients, age, female, body weight, duration of surgery and detail methods in each group etc. Data have been extracted independently by two 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 at 30 min and number of additional analgesics. Secondary outcomes include pain scores at 1 h, pain scores at 6 h, time of first analgesic requirement, and additional analgesic consumption.

Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale [20]. 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 [21].

Statistical analysis

We estimate the standard mean difference (SMD) with 95% confidence interval (CI) for continuous outcomes (pain scores at 30 min, pain scores at 1 h, pain scores at 6 h, time of first analgesic requirement and additional analgesic consumption) and odd ratio (OR) with 95% CIs for dichotomous outcomes (number of additional analgesics). The random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity [19, 22]. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting one 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).

Results

Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in Fig. 1. 132 potentially relevant articles are identified initially. Finally, four RCTs that meet our inclusion criteria are included in the meta-analysis [15–17, 23].

The baseline characteristics of the four eligible RCTs in the meta-analysis are summarized in Table 1. The three studies are published between 2001 and 2020, and total sample size is 172. Among the four studies included here, two studies report pain scores at 30 min [17, 23], two studies report number of additional analgesics [15, 23], three studies report pain scores at 1 h [16, 17, 23], two studies report pain scores at 6 h [17, 23], three studies report time of first analgesic requirement [15–17], and two studies report additional analgesic consumption [17, 23]. Jadad scores of the four included studies vary from 3 to 5, and all four studies are considered to be high-quality ones according to quality assessment.

Table 1
Characteristics of included studies

| NO. | Author | Ketamine supplementation group | | | | | | Control group | | | | | |
|-----|-----------------|--------------------------------|-------------|------------|-------------|---------------------------|---|---------------|-------------|------------|-------------|---------------------------|---|
| | | Number | Age (years) | Female (n) | Weight (kg) | Duration of surgery (min) | Methods | Number | Age (years) | Female (n) | Weight (kg) | Duration of surgery (min) | Methods |
| 1 | Sağır 2020 | 25 | 48.6 ± 13.3 | 11 | 78.9 ± 15.2 | 37.2 ± 15.2 | 1 mg/kg ketamine intraarticularly plus bupivacaine | 25 | 45.3 ± 14.4 | 16 | 78.0 ± 11.8 | 49.0 ± 17.5 | placebo plus bupivacaine |
| 2 | Saricaoglu 2005 | 15 | 31 ± 8 | 6 | - | - | intravenous ketamine (0.5 mg/kg/h) during the surgery plus spinal anesthesia with 12.5 mg bupivacaine | 15 | 30 ± 7 | 5 | - | - | placebo plus spinal anesthesia with 12 mg bupivacaine |
| 3 | Batra 2005 | 22 | 35 ± 4 | 4 | 72 ± 4 | - | intra-articular 1.0 mg/kg ketamine plus bupivacaine | 20 | 44 ± 3 | 4 | 68 ± 3 | - | placebo plus bupivacaine |
| 4 | Menigaux 2001 | 25 | 37 ± 9 | 8 | 76 ± 13 | 30 ± 6 | intravenous 0.15 mg/kg ketamine plus bupivacaine | 25 | 36 ± 12 | 9 | 73 ± 14 | 30 ± 10 | placebo plus bupivacaine |

Primary outcomes: pain scores at 30 min and number of additional analgesics

These outcome data are analyzed with the random-effects model, and compared to control group for knee arthroscopy, ketamine supplementation is associated with significantly reduced pain scores at 30 min (SMD=-0.98; 95% CI=-1.42 to -0.55; $P < 0.00001$) with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $P = 0.92$) (Fig. 2) and number of additional analgesics (OR = 0.27; 95% CI = 0.10 to 0.71; $P = 0.008$) with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $P = 0.87$) (Fig. 3).

Sensitivity analysis

No heterogeneity is observed for these outcomes and thus we do not perform sensitivity analysis via omitting one study in turn to detect the heterogeneity.

Secondary outcomes

In comparison with control group for knee arthroscopy, ketamine supplementation shows no obvious impact on pain scores at 1 h (SMD=-1.34; 95% CI=-3.42 to 0.73; $P = 0.20$; Fig. 4), pain scores at 6 h (SMD=-0.33; 95% CI=-1.39 to 0.72; $P = 0.53$; Fig. 5), time of first analgesic requirement (SMD = 1.27; 95% CI=-0.95 to 3.49; $P = 0.26$; Fig. 6) or additional analgesic consumption (SMD=-2.25; 95% CI=-5.89 to 1.40; $P = 0.23$; Fig. 7).

Discussion

Knee arthroscopic surgery can result in moderate to severe pain because of the insertion of arthroscopic instruments into the joint, bone removal, soft tissue dissection and distention [24–28]. One study compared the analgesic effect of tramadol, magnesium, and ketamine after arthroscopic meniscectomy, and unraveled that 1 mg/kg intraarticular ketamine reduced additional analgesic requirement and facilitated early mobilization [29]. In addition, 0.5 mg/kg ketamine was documented to improve the analgesic efficacy of both tramadol and ropivacaine on pain management after arthroscopic meniscectomy [30].

However, supplementation with ketamine to bupivacaine reported conflicting results for the analgesia of knee arthroscopy [16, 17, 23]. Our meta-analysis has included four RCTs and 172 patients. The results reveals that ketamine supplementation to bupivacaine can significantly reduce the pain scores at 30 min and number of additional analgesics after knee arthroscopy, but showed no obvious impact on pain scores at 1 h, pain scores at 6 h, time of first analgesic requirement or additional analgesic consumption. In addition, one RCT reported the similar incidence of adverse events such as postoperative nausea and vomiting, urinary retention and pruritus [15].

Considering the sensitivity analysis, although there is no significant heterogeneity, several factors may result in some bias. Firstly, different administration routes are included, such as intraarticular [15, 17] and intravenous [16, 23] approaches. Secondly, the doses of ketamine range from 0.15 mg/kg to 1.0 mg/kg, which may affect the efficacy assessment. Thirdly, various operation procedures during knee arthroscopy are associated with different pain intensity, and may have some impact on the analgesia of ketamine supplementation.

This meta-analysis has several potential limitations. Firstly, our analysis is based on four RCTs, and all of them have a relatively small sample size ($n < 100$). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Next, although there is no significant heterogeneity, different administration routes and doses of ketamine supplementation may produce some bias. Finally, it is not feasible to perform the meta-analysis of some important index such as pain scores at longer follow up time and perform the subgroup analysis based on dosages due to the limited studies.

Conclusions

Ketamine supplementation to bupivacaine may be effective to improve the analgesia of knee arthroscopy.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

Chunhong Li conducted the design, Zhibo Xiao and Liuli Chen conducted the study planning, data analysis and data interpretation, Songli Pan wrote and revised the article. All authors read and approved the final manuscript.

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Chunhong Li¹ PHD, Zhibo Xiao² PHD, Liuli Chen¹ PHD, Songli Pan³ PHD

¹Operating room of the First Affiliated Hospital of Hainan Medical University, China;

²Department of anesthesiology, The First Affiliated Hospital of Hainan Medical University, China;

³Department of Spinal Surgery, The First Affiliated Hospital of Hainan Medical University, China;

Chunhong Li: 47242811@qq.com, Zhibo Xiao: xzb32@163.com, Liuli Chen: 664941581@qq.com, Songli Pan: ed7713@163.com;

*Corresponding author: Songli Pan

The First Affiliated Hospital of Hainan Medical University, China;

Telephone numbers: 023-63501832;

Fax Number: 023-63501832;

E-mail: ed7713@163.com;

References

- [1] B.A. Basques, B.M. Saltzman, S.S. Korber, I.K. Bolia, E.N. Mayer, B.R. Bach, N.N. Verma, B.J. Cole, A.E. Weber, Resident Involvement in Arthroscopic Knee Surgery Is Not Associated With Increased Short-term Risk to Patients, *Orthopaedic journal of sports medicine* 8(12) (2020) 2325967120967460.
- [2] R. Sihvonen, M. Paavola, A. Malmivaara, A. Itälä, A. Joukainen, J. Kalske, H. Nurmi, J. Kumm, N. Sillanpää, T. Kiekara, A. Turkiewicz, P. Toivonen, M. Englund, S. Taimela, T.L.N. Järvinen, Arthroscopic partial meniscectomy for a degenerative meniscus tear: a 5 year follow-up of the placebo-surgery controlled FIDELITY (Finnish Degenerative Meniscus Lesion Study) trial, *British journal of sports medicine* 54(22) (2020) 1332-1339.
- [3] D.L. Jones, P. Neff, D.B. Franklin, 3rd, J.B. Reid, 3rd, Arthroscopic Posterior Capsular Release for Loss of Knee Extension, *Arthroscopy techniques* 9(10) (2020) e1439-e1446.
- [4] J.R. Pedersen, E.M. Roos, J.B. Thorlund, B. Terluin, L.H. Ingelsrud, Cutoff Values to Interpret Short-term Treatment Outcomes After Arthroscopic Meniscal Surgery, Measured With the Knee Injury and Osteoarthritis Outcome Score, *The Journal of orthopaedic and sports physical therapy* 51(6) (2021) 281-288.
- [5] O. Atik, Should degenerative horizontal tear of the medial meniscus be treated with surgery?, *Eklemler hastalıkları ve cerrahisi = Joint diseases & related surgery* 29(2) (2018) 63-4.
- [6] G. Glogovac, M. Kennedy, M.D. Parman, K.A. Bowers, A.J. Colosimo, B.M. Grawe, Opioid Requirement following Arthroscopic Knee Surgery: Are There Predictive Factors Associated with Long-Term Use, *The journal of knee surgery* 34(8) (2021) 810-815.
- [7] N.M. Elsharnouby, H.E. Eid, N.F. Abou Elezz, A.N. Moharram, Intraarticular injection of magnesium sulphate and/or bupivacaine for postoperative analgesia after arthroscopic knee surgery, *Anesthesia and analgesia* 106(5) (2008) 1548-52, table of contents.
- [8] C. Caparrini, I. Miniati, M. Ponti, A. Baldini, Perioperative pain management in fast-track knee arthroplasty, *Acta bio-medica : Atenei Parmensis* 88(2s) (2017) 139-144.
- [9] M.J. Hartwell, R.S. Selley, M.A. Terry, V.K. Tjong, Can We Eliminate Opioid Medications for Postoperative Pain Control? A Prospective, Surgeon-Blinded, Randomized Controlled Trial in Knee Arthroscopic Surgery, *The American journal of sports medicine* 48(11) (2020) 2711-2717.
- [10] B.M. Block, S.S. Liu, A.J. Rowlingson, A.R. Cowan, J.J.A. Cowan, C.L. Wu, Efficacy of Postoperative Epidural Analgesia A Meta-analysis, *JAMA* 290(18) (2003) 2455-2463.
- [11] V.K.F. Kong, M.G. Irwin, Gabapentin: a multimodal perioperative drug?, *BJA: British Journal of Anaesthesia* 99(6) (2007) 775-786.
- [12] A.B. Petrenko, T. Yamakura, H. Baba, K. Shimoji, The role of N-methyl-D-aspartate (NMDA) receptors in pain: a review, *Anesthesia and analgesia* 97(4) (2003) 1108-16.
- [13] X. Yu, J.B. Sessle, A.D. Haas, A. Izzo, H. Vernon, W.J. Hu, Involvement of NMDA receptor mechanisms in jaw electromyographic activity and plasma extravasation induced by inflammatory irritant application to temporomandibular joint region of rats, *Pain* 68(1) (1996) 169-178.
- [14] M. Tverskoy, M. Oren, M. Vaskovich, I. Dashkovsky, I. Kissin, Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: a study in postoperative patients, *Neuroscience letters* 215(1) (1996) 5-8.
- [15] Ö. Sağır, B. Tatar, F. Uğün, H.F. Demir, A.N. Balkaya, G. Meriç, N. Kocaoğlu, A. Köroğlu, Effects of intraarticular ketamine combined with periarticular bupivacaine on postoperative pain after arthroscopic meniscectomy, *Joint diseases and related surgery* 31(3) (2020) 589-596.
- [16] F. Saricaoglu, D. Dal, A.E. Salman, M.N. Doral, K. Kiliç, U. Aypar, Ketamine sedation during spinal anesthesia for arthroscopic knee surgery reduced the ischemia-reperfusion injury markers, *Anesthesia and analgesia* 101(3) (2005) 904-9, table of contents.
- [17] Y.K. Batra, R. Mahajan, S.K. Bangalia, O.N. Nagi, M.S. Dhillon, Bupivacaine/ketamine is superior to intra-articular ketamine analgesia following arthroscopic knee surgery, *Canadian journal of anaesthesia = Journal canadien d'anesthésie* 52(8) (2005) 832-6.
- [18] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, *Journal of clinical epidemiology* 62(10) (2009) 1006-12.
- [19] J. Zhao, W. Huang, S. Zhang, J. Xu, W. Xue, B. He, Y. Zhang, Efficacy of Glutathione for Patients With Cystic Fibrosis: A Meta-analysis of Randomized-Controlled Studies, *American Journal of Rhinology & Allergy* (2019) 1945892419878315.

- [20] A.R. Jadad, R.A. Moore, D. Carroll, C. Jenkinson, D.J.M. Reynolds, D.J. Gavaghan, H.J. McQuay, Assessing the quality of reports of randomized clinical trials: Is blinding necessary?, *Controlled Clinical Trials* 17(1) (1996) 1-12.
- [21] L.L. Kjaergard, J. Villumsen, C. Gluud, Reported Methodologic Quality and Discrepancies between Large and Small Randomized Trials in Meta-Analyses, *Annals of Internal Medicine* 135(11) (2001) 982-989.
- [22] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, *Statistics in medicine* 21(11) (2002) 1539-58.
- [23] C. Menigaux, B. Guignard, D. Fletcher, D.I. Sessler, X. Dupont, M. Chauvin, Intraoperative small-dose ketamine enhances analgesia after outpatient knee arthroscopy, *Anesthesia and analgesia* 93(3) (2001) 606-12.
- [24] I.B. Botser, T.W. Smith, Jr., R. Nasser, B.G. Domb, Open surgical dislocation versus arthroscopy for femoroacetabular impingement: a comparison of clinical outcomes, *Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association* 27(2) (2011) 270-8.
- [25] C. 29162135Li, J. Qu, Efficacy of dexmedetomidine for pain management in knee arthroscopy: A systematic review and meta-analysis, *Medicine* 96(43) (2017) e7938.
- [26] F.A. Tepolt, J. Bido, S. Burgess, L.J. Micheli, M.S. Kocher, Opioid Overprescription After Knee Arthroscopy and Related Surgery in Adolescents and Young Adults, *Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association* (2018).
- [27] D. Tong, F. Chung, Postoperative pain control in ambulatory surgery, *The Surgical clinics of North America* 79(2) (1999) 401-30.
- [28] X. Chen, X. Mou, Z. He, Y. Zhu, The effect of midazolam on pain control after knee arthroscopy: a systematic review and meta-analysis, *Journal of orthopaedic surgery and research* 12(1) (2017) 179.
- [29] N. Salman, B. Olgunkeleş, U. Bektaş, D. Güner, M. Bektas, Ş. Ay, S. Şekerci, Effects of intraarticular tramadol, magnesium and ketamine on postoperative pain in arthroscopic meniscectomy, *Brazilian journal of anesthesiology (Elsevier)* 69(1) (2019) 35-41.
- [30] H. Ayoglu, H. Altunkaya, A. Bayar, I.O. Turan, Y. Ozer, A. Ege, The effect of intraarticular combinations of tramadol and ropivacaine with ketamine on postoperative pain after arthroscopic meniscectomy, *Archives of orthopaedic and trauma surgery* 130(3) (2010) 307-12.

Figures

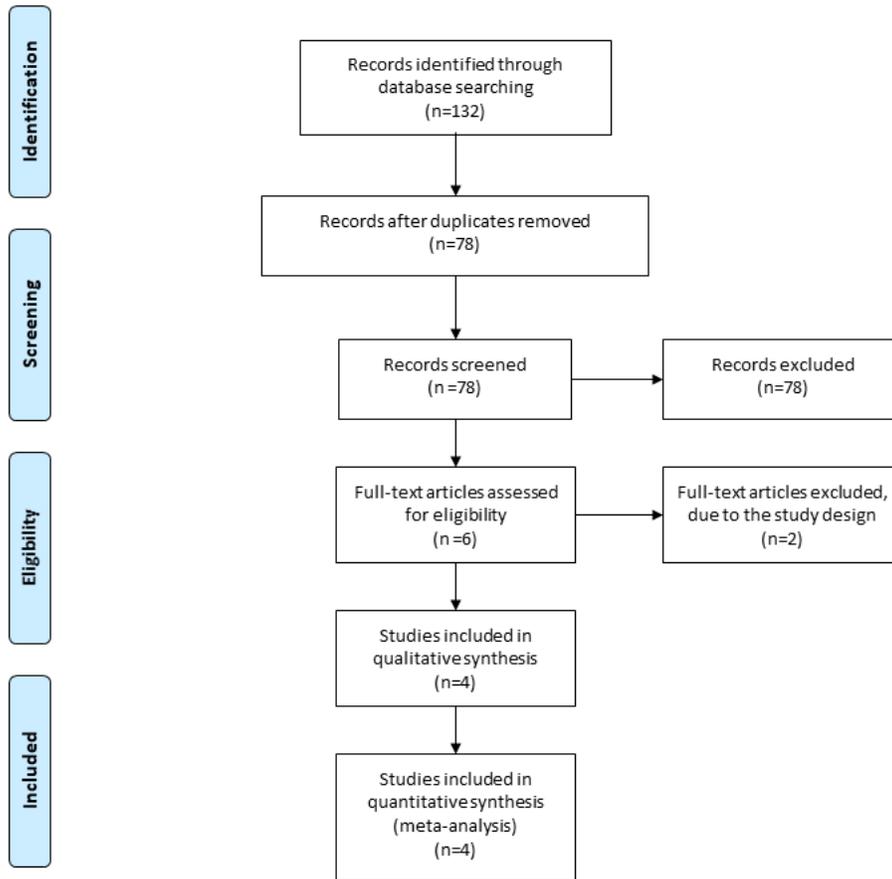


Figure 1

Flow diagram of study searching and selection process.

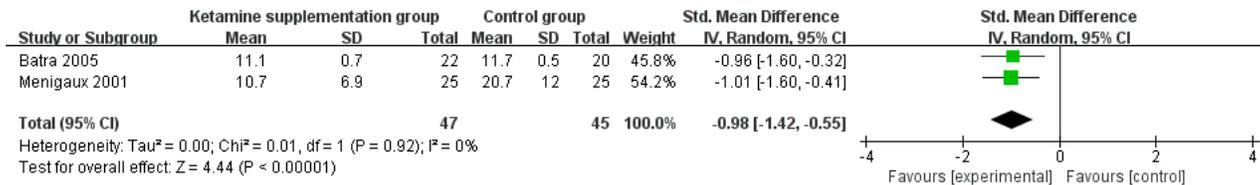


Figure 2

Forest plot for the meta-analysis of pain scores at 30 min.

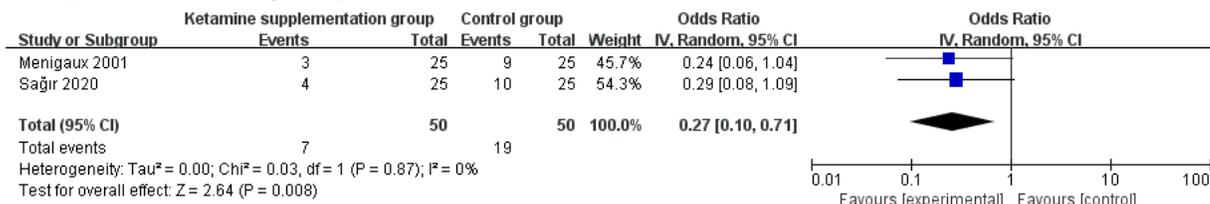


Figure 3

Forest plot for the meta-analysis of number of additional analgesics.

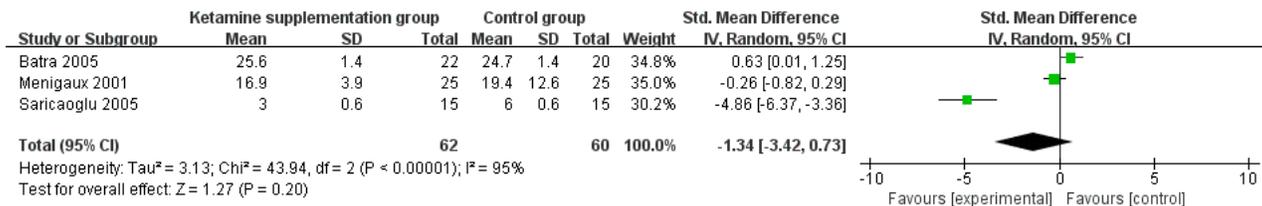


Figure 4

Forest plot for the meta-analysis of pain scores at 1 h.

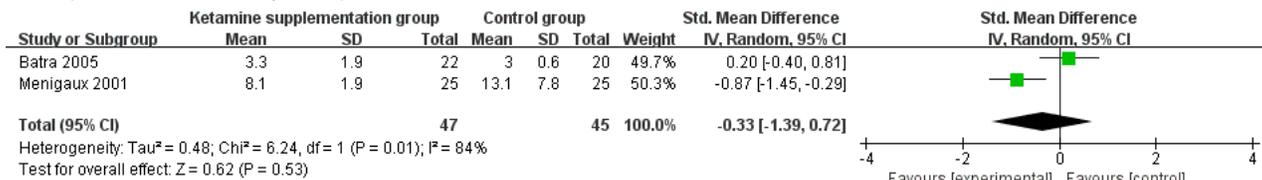


Figure 5

Forest plot for the meta-analysis of pain scores at 6 h.

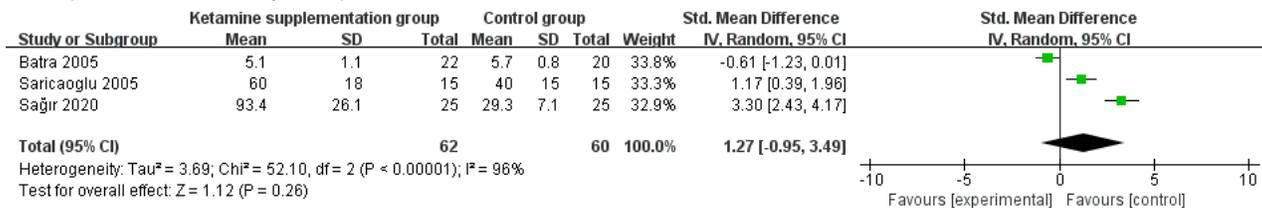


Figure 6

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

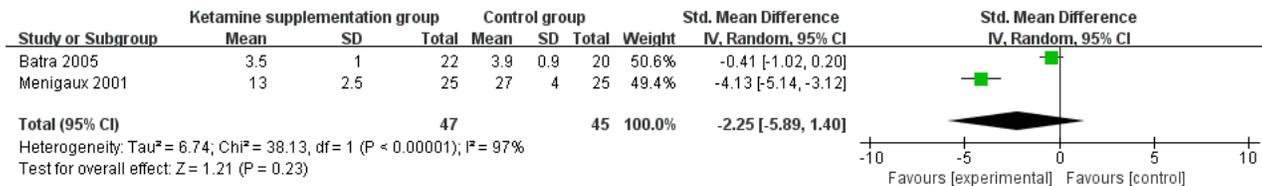


Figure 7

Forest plot for the meta-analysis of additional analgesic consumption.