The Journal of Arthroplasty 37 (2022) 1688–1690

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Practice Guidelines

Ketamine in Total Joint Arthroplasty: The Clinical Practice Guidelines of the American Association of Hip and Knee Surgeons, American Society of Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society

Charles P. Hannon, MD, MBA [a, *], Yale A. Fillingham, MD [b], Jeremy M. Gililland, MD [c], Scott M. Sporer, MD [d], William G. Hamilton, MD [j, 1], Craig J. Della Valle, MD [d, 1], AAHKS Anesthesia & Analgesia Clinical Practice Guideline Workgroup

[a] Department of Orthopedic Surgery, Washington University in St. Louis, St. Louis, MO
[b] Rothman Institute at Thomas Jefferson University, Philadelphia, PA
[c] Department of Orthopaedic Surgery, University of Utah, Salt Lake City, UT
[d] Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL
[j] Anderson Orthopedic Research Institute, Alexandria, VA

ARTICLE INFO

Article history:
Received 25 January 2022
Accepted 19 February 2022
Available online 31 March 2022

Keywords:
ketamine
total joint arthroplasty
total knee arthroplasty
total hip arthroplasty
multimodal analgesia

The American Association of Hip and Knee Surgeons (AAHKS), The American Academy of Orthopaedic Surgeons (AAOS), The Hip Society, The Knee Society, and The American Society of Regional Anesthesia and Pain Medicine (ASRA) collaborated to develop evidence-based guidelines on the use of ketamine in primary total joint arthroplasty (TJA). The purpose of these guidelines is to improve the treatment of primary TJA patients and reduce practice variation by promoting a multidisciplinary, evidence-based approach to the use of ketamine in primary TJA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of ketamine in primary TJA. Utilizing the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, the committee members completed a systematic review and meta-analyses to support the clinical practice guidelines [1]. Direct meta-analyses were performed when the data allowed, but network meta-analyses were not performed. Network meta-analyses are limited in their ability to control for significant variation, particularly in the multimodal analgesic protocols utilized, and the time points outcomes were reported. The current clinical practice guidelines were based on the best available evidence, so future updates may become necessary as additional literature becomes available with new research.

Guideline Question 1

For patients undergoing primary TJA, does perioperative ketamine affect postoperative pain, opioid consumption, and/or complications after surgery?

Response/Recommendation 1A

Ketamine administered intraoperatively decreases postoperative opioid consumption.

Strength of Recommendation

Strong.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2022.02.122.

* Address correspondence to: Charles P. Hannon MD, MBA, Department of Orthopedic Surgery, Washington University in St. Louis, St. Louis, MO.

https://doi.org/10.1016/j.arth.2022.02.122

Response/Recommendation 1B

Ketamine administered intraoperatively may decrease postoperative pain and reduce postoperative nausea and vomiting.

Strength of Recommendation

Moderate.

Response/Recommendation 1C

Ketamine administered intraoperatively is not associated with an increase in adverse events in most patients. However, intraoperative ketamine may lead to an increased risk of delirium and hallucinations among elderly patients after surgery.

Strength of Recommendation

Moderate.

Rationale

Six high-quality studies evaluated the influence of intraoperative ketamine on opioid consumption after primary TJA [2–7]. Three of these studies also included a postoperative ketamine intravenous infusion for 24 hours [2,3,6]. Five of the six studies found reduced postoperative opioid consumption after primary TJA when intraoperative ketamine was administered [2–6]. The one study that did not demonstrate this finding from Tan et al. compared intraoperative ketamine administered at 6 mcg/kg/minute to placebo and found no difference in opioid consumption at 24 hours postoperatively. Due to heterogeneity in the dosing of ketamine administered intraoperatively, we were unable to conduct a meta-analysis.

Seven high-quality studies evaluated the influence of intraoperative ketamine on pain after primary TJA [2–8]. Four of these studies also included a postoperative ketamine infusion for 24 hours [2,3,6,8]. Four studies, two intraoperative only and two intraoperative plus postoperative ketamine, found decreased pain in the first 48 hours after primary TJA [3,4,7,8]. The three other studies found no difference in postoperative pain between ketamine and placebo at all time points [2,5,6]. Although all studies that evaluated postoperative pain are of high quality, the workgroup downgraded this recommendation to moderate because of the mixed evidence on the influence of intraoperative ketamine on postoperative pain.

Four high-quality studies evaluated the effects of intraoperative ketamine on postoperative nausea and vomiting [4–6,8]. A meta-analysis of these four studies with limited heterogeneity ($I^2 = 4.9\%$) found that ketamine significantly reduces postoperative nausea and vomiting. (0.68 relative risk [RR]; 95% confidence interval [CI] 0.50 to 0.92). The workgroup downgraded this recommendation to moderate as this is not the primary purpose of intraoperative ketamine. While the antiemetic effect is a beneficial secondary effect of ketamine, ketamine is primarily used as an anesthetic for sedation and as an analgesic for pain control.

Four high-quality studies evaluated the adverse effects of intraoperative ketamine for primary TJA [4–6,8]. All four studies found no increase in adverse events with the use of intraoperative ketamine, including delirium and urinary retention. A meta-analysis of three studies with no heterogeneity ($I^2 = 0$) found no increased risk of postoperative delirium with intraoperative ketamine administration (0.70 RR; 95% CI 0.29 to 1.69) [4–6]. Another meta-analysis of three studies with no heterogeneity ($I^2 = 0$) found no increased risk of postoperative urinary retention with intraoperative ketamine administration (1.02 RR; 95% CI 0.53 to 1.94) [5,6,8]. Although the meta-analyses demonstrate no increased risk of postoperative delirium or postoperative urinary retention, the rarity of the event makes it more difficult to study in randomized clinical trials. Database studies might be better suited to evaluate rare adverse events such as delirium. Two database studies have evaluated the association between intraoperative ketamine and delirium, with conflicting results between the studies [9,10]. The authors were unable to determine a threshold dose of intraoperative ketamine beyond which the risk of delirium increases. In addition to these studies in TJA, the largest trial conducted of 672 surgical patients found that patients 60 and older had a higher rate of hallucinations and nightmares after surgery with ketamine used intraoperatively than without [11]. As a result, the workgroup recommends using intraoperative ketamine with caution in elderly patients as it may be associated with an increased risk of psychomimetic adverse events postoperatively.

Areas for Future Research

The best available evidence on ketamine in primary TJA includes high-quality data; however, there remain limitations in the formulation of this clinical practice guideline. A majority of studies published on the use of ketamine in TJA evaluate intravenous ketamine administered intraoperatively. However, several of these studies included a postoperative ketamine infusion for up to 48 hours postoperatively. With the evolution of modern multimodal analgesia and anesthetic protocols, along with decreasing length of stay, postoperative infusions of anesthetics such as ketamine are not commonly utilized. In addition, there is significant variation in the dosing of ketamine utilized in the studies included in this clinical practice guideline. Further studies are warranted to determine the optimal clinical dose of ketamine that maximizes the anesthetic and analgesic effects while minimizing postoperative side effects. In addition, with the shift to outpatient TJA, further research should investigate the role of ketamine for same-day surgery.

Peer Review Process

Following the committee's formulation of the Clinical Practice Guideline draft, it underwent a peer review by the board of directors from AAHKS, ASRA, and the Hip and Knee Societies. The AAOS Evidence-Based Quality and Value Committee reviewed the Clinical Practice Guideline draft for endorsement. Additionally, the publication of the systematic review and meta-analysis on opioids in primary hip and knee arthroplasties that supported the formulation of the Clinical Practice Guideline has undergone peer review for publication.

Disclosure Requirement

All authors or contributors to the Clinical Practice Guideline have provided a disclosure statement in accordance with the publicly available AAOS Orthopedic Disclosure Program. All authors and contributors attest none of the disclosures present are relevant to the Clinical Practice Guidelines. In accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, all authors and contributors attest none of the current disclosures are relevant to the Clinical Practice Guidelines, and no prior relevant financial conflict was within a year of initiating work on the guideline.

FDA Clearance Statement

According to the FDA, it is the prescribing physician's responsibility to ascertain the FDA clearance status for all medications prior to use in a clinical setting.

Acknowledgments

We would like to thank AAHKS for providing the funding and administrative support. We would like to thank Jayson Murray, Nicole Nelson, and Francisco Casambre from the AAOS Department of Research, Quality, and Scientific Affairs for their assistance with the analysis and guidance. Lastly, we thank the leadership of the AAHKS, AAOS, ASRA, and the Hip and Knee societies for help with organizational support.

References

[1] American Academy of Orthoapedic Surgeons (AAOS) AAOS clinical practice guideline and systematic review methodology. https://www.aaos.org/quality/research-resources/methodology/; 2017 [accessed 01.05.20].

[2] Adam F, Chauvin M, Manoir BD, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. Anesth Analg 2005;100:475–80. https://doi.org/10.1213/01.ane.0000142117.82241.dc.

[3] Aveline C, Roux AL, Hetet HL, Gautier JF, Vautier P, Cognet F, et al. Pain and recovery after total knee arthroplasty. Clin J Pain 2014;30:749–54. https://doi.org/10.1097/ajp.0000000000000033.

[4] Cengiz P, Gokcinar D, Karabeyoglu I, Topcu H, Cicek GS, Gogus N. Intraoperative low-dose ketamine infusion reduces acute postoperative pain following total knee replacement surgery: a prospective, randomized double-blind placebo-controlled trial. J Coll Physicians Surg Pak 2014;24:299–303.

[5] Martinez V, Cymerman A, Ammar SB, Fiaud JF, Rapon C, Poindessous F, et al. The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: a randomised, double-blind, controlled study. Anaesthesia 2014;69:46–52. https://doi.org/10.1111/anae.12495.

[6] Remérand F, Tendre CL, Baud A, Couvret C, Pourrat X, Favard L, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. Anesth Analg 2009;109:1963–71. https://doi.org/10.1213/ane.0b013e3181bdc8a0.

[7] Tan TL, Longenecker AS, Rhee JH, Good RP, Emper WD, Freedman KB, et al. Intraoperative ketamine in total knee arthroplasty does not decrease pain and narcotic consumption: a prospective randomized controlled trial. J Arthroplasty 2019;34:1640–5. https://doi.org/10.1016/j.arth.2019.04.017.

[8] Aveline C, Gautier JF, Vautier P, Cognet F, Hetet HL, Attali JY, et al. Postoperative analgesia and early rehabilitation after total knee replacement: a comparison of continuous low-dose intravenous ketamine versus nefopam. Eur J Pain 2009;13:613–9. https://doi.org/10.1016/j.ejpain.2008.08.003.

[9] Weinstein SM, Poultsides L, Baaklini LR, Mörwald EE, Cozowicz C, Saleh JN, et al. Postoperative delirium in total knee and hip arthroplasty patients: a study of perioperative modifiable risk factors. Br J Anaesth 2018;120:999–1008. https://doi.org/10.1016/j.bja.2017.12.046.

[10] Memtsoudis S, Cozowicz C, Zubizarreta N, Weinstein SM, Liu J, Kim DH, et al. Risk factors for postoperative delirium in patients undergoing lower extremity joint arthroplasty: a retrospective population-based cohort study. Reg Anesth Pain Med 2019;44:934. https://doi.org/10.1136/rapm-2019-100700.

[11] Avidan MS, Maybrier HR, Abdallah AB, Jacobsohn E, Vlisides PE, Pryor KO, et al. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. Lancet 2017;390:267–75. https://doi.org/10.1016/s0140-6736(17)31467-8.