Analgesia strategy on cognitive impairment after spinal anesthesia in hip surgery: A meta-analysis

Running title: The effect of spinal anesthesia on cognitive impairment after hip surgery

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Abstract

Background: Previous studies have indicated no significant difference in the incidence of cognitive impairment between general anesthesia and spinal anesthesia for hip surgery. However, the debate between general and spinal anesthesia merely scratches the surface. Within spinal anesthesia, components like pre- or post-surgery analgesia warrant consideration in optimizing strategies for geriatric patients. Hence, our study aims to analyze cognitive impairment incidence across various analgesia strategies as adjuncts to spinal anesthesia for hip surgery.

Methods: We systematically conducted a search across two databases for randomized trials that investigated the incidence of cognitive impairment following hip surgery with spinal anesthesia. We analyzed pooled data for distinct pre or post-operative analgesia approaches. The primary outcome of this review was the occurrence of post-operative delirium (POD) within 7 days post-surgery and delayed neurocognitive recovery (DNCR), defined as cognitive impairment within the first 30 days after surgery.

Results: A systematic search yielded 13 studies comparing analgesia modalities. Based on our meta-analysis results, we demonstrated that adequate analgesia administration could decrease the incidence of POD (RR: 0.37, 95% CI: 0.20 – 0.68; $p < 0.05$, moderate quality of evidence), DNCR at 24 hours post-operatively, 72 hours, and 4-7 days post-operatively.

Conclusion: Optimizing perioperative analgesia are beneficial in reducing the risk of cognitive impairment in elderly patients undergoing hip surgery with spinal anesthesia.

Keywords: *Post-operative cognitive dysfunction; delirium; post-operative analgesia; regional anesthesia; geriatric*.

INTRODUCTION

The relationship between anesthesia strategies and cognitive impairment after surgery has been a subject of extensive investigation. Recent revisions in terminology have refined our understanding of cognitive impairment associated with anesthesia and surgery (1). Post-operative Cognitive Dysfunction (POCD) is now recognized as a neurocognitive disorder, defined according to DSM-V criteria, manifesting between 30 days to 1 year post-surgery and anesthesia, provided no other conditions account for the decline in cognitive function (2). Conversely, cognitive impairment occurring within the initial 30 days encompasses post-operative delirium (POD) and delayed neurocognitive recovery (DNCR). POD represents a specific subset of delirium distinct from emergence from anesthesia, typically occurring within the first 72 hours post-operatively.

Advanced age (> 70 years old) has consistently been associated with an increased risk of POD (3). Notably, a substantial portion of patients undergoing hip surgery fall within the elderly demographic. Prior study has shown no significant disparity in cognitive impairment incidence between general anesthesia (GA) and spinal anesthesia (SA) for hip surgery (4). Nevertheless, SA offers advantages over GA by mitigating blood loss (5), which itself elevates the risk of POD (6,7).

However, the debate between GA and SA merely scratches the surface. Within spinal anesthesia, components like intraoperative pre- or post-surgery analgesia warrant consideration in optimizing strategies for geriatric patients. Postoperative pain has been implicated in cognitive impairment risk (8), with opioid use further associated with increased postoperative delirium risk, emphasizing the preference for multimodal analgesia to minimize opioid use (9). Hence, our study aims to analyze cognitive impairment incidence across various analgesia strategies as adjuncts to spinal anesthesia for hip surgery.

MATERIALS AND METHODS

We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We systematically searched two databases, including PUBMED and CENTRAL. Following the database searches, three authors independently screened all randomized trials that investigated the impact of various spinal anesthesia strategies on cognitive impairment in hip surgery. Hip surgery encompassed both elective and emergency procedures for hip fracture and hip replacement. In cases of disagreement between the two authors, a third author made the final decision.

All selected studies were assessed for full-text availability, and relevant data were extracted. This data included the number of participants, average participant age, gender distribution, methods of randomization and blinding, surgical duration, blood loss volume, the specific spinal anesthesia and comparative anesthesia strategies employed, the post-operative analgesia regimen, criteria and measurement methods for delirium and cognitive impairment, the timing of outcome measurements, and data related to the intended outcomes. Studies lacking the desired outcomes and those without both group receiving spinal anesthesia were excluded. Additionally, studies comparing different doses of local anesthesia were also excluded.

The primary objective of this systematic review was to assess the incidence of POD within 7 days post-surgery and DNCR, defined as cognitive impairment occurring within 30 days after surgery. Secondary outcomes encompassed post-operative cognitive disorder (POCD), characterized by cognitive impairment within 30 days to 1 year after surgery. We analyzed pooled data for various peri-operative analgesia comparison. We compared the peri-operative analgesia strategy into superior and inferior analgesia if differences in pain intensity scores were found among treatment groups in the study.

For the analysis, risk ratios (RR) were used for dichotomous data, and standardized mean differences (SMD) were used for continuous data. We employed the Mantel-Haenszel fixed-effect method for dichotomous data and the inverse variance random-effect method for continuous data through the RevMan 5.4.1 software. Heterogeneity among studies was evaluated using the X^2 test.

Two reviewers independently assessed the risk of bias in included studies using the Cochrane Collaboration tool for assessing the risk of bias in randomized controlled trials (RCTs) (10). The quality of evidence (QOE) for each outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (11). Funnel plot asymmetry tests were conducted for outcomes involving more than ten studies in the meta-analysis, with the results interpreted alongside visual inspection of the funnel plot.

RESULTS

A systematic search yielded a total of 277 literature sources after removing duplicates. However, only 74 studies were included after the initial screening process. Subsequently, 61 studies were excluded after obtaining their full texts, with reasons displayed in Figure 1. Ultimately, 13 trials were included in this systematic review (12–24).

Studies that did not implement double-blinding were judged to have some concern of bias. This judgment was based on the notion that knowledge of the intervention did not likely influence the assessment of these outcomes. The GRADE evaluations of the included studies are shown in Table 2. We considered some inconsistencies in only in one outcome which is DNCR at 72h post-operatively due to substantial heterogeneity. Therefore, we downgrade these outcomes to one level. There were no issues with indirectness in any of the outcomes. We did not downgrade all outcomes for imprecision because the upper or lower confidence limit did not cross a risk ratio (RR) reduction of 25% in either direction.

Different analgesia modalities were used in each included study, with no consistency among them. Therefore, an analysis could not be performed for the comparison of analgesia modalities. Instead, we conducted an analysis comparing groups receiving superior analgesia to control or inferior analgesia. Our meta-analysis results showed that adequate analgesia administration could decrease the incidence of delirium, DNCR at 24 hours post-operatively, 72 hours, and 4-7 days post-operatively (Table 1).

According to Table 3, two studies implemented a treatment without perioperative parenteral opioid administration in one of the comparison groups. The first study by Li et al utilized an opioid-sparing strategy through the use of continuous peripheral nerve blocks starting from admission until the post-operative period (14). The results showed differences in MMSE scores at 24 hours (25.63±2.50 vs. 23.97±2.62, $p < 0.05$) and 72 hours postoperatively (27.76±1.79 vs. 25.34±1.91, $p < 0.05$) compared to the group receiving PCA opioids. The second study by Xu et al employed an opioid-sparing strategy through the use of intrathecal morphine (18). The incidence of delirium was lower (2 vs. 6, $p < 0.05$), and the DRS-r98 scores were significantly lower up to 48 hours postoperatively in the opioid-sparing group compared to those receiving PCA opioids.

Two studies avoided intravenous opioid administration by utilizing a strategy of peripheral block instead of intravenous paracetamol. The first study by Yamamoto et al only used NSAIDs as post-operative analgesia, resulting in differences in analgesia adequacy post-operatively in both groups at the 12-hour post-operative measurement (19). This was due to the wearing-off effect of spinal anesthesia combined with the adequacy of the analgesic effect from the peripheral block. The incidence of delirium was lower (2 vs. 4) in the peripheral block group. Meanwhile, the second study by Uysal et al employed PCEA as the post-operative analgesia modality in both groups (24). Therefore, no differences were observed between the two groups in the second study. Interestingly, the incidence of delirium was also lower (5 vs. 9) in the peripheral block group. In

contrast to the first study, the second study initiated peripheral blocks upon admission in the control group and repeated them every 8 hours until the day of surgery, resulting in differences in analgesia adequacy in the preoperative period compared to the control group.

DISCUSSION

Our study reported that adequate analgesia can reduce the incidence of delirium and DNCR. This was consistent with the results of a prospective cohort study reporting that severe post-operative pain increases the risk 9-fold (RR 9.0, 95% CI 1.8-45.2) for delirium in patients undergoing surgery for hip fracture (25). Regarding the choice of analgesia modality, the higher the opioid administration, the higher the likelihood of causing POD (26). Meperidine is the opioid most at risk of causing POD (27). Therefore, analgesia modalities with opioid-sparing strategies can reduce the risk of cognitive impairment after surgery (28). Analgesia using regional analgesia modalities was effective in reducing DNCR (OR 0.46, 95% CI 0.35-0.59) compared to systemic analgesia modalities in patients undergoing major non-cardiac surgery (29). The use of peripheral nerve blocks (PNBs) in hip arthroplasty and knee replacement, regardless of anesthesia type, has been reported to significantly reduce the risk of postoperative delirium (13). This is also supported by similar results for the incidence of POD (RR 0.60, 95% CI 0.38-0.94) in a systematic review of patients undergoing hip surgery (30).

Surgical trauma-induced stress, including perioperative pain, can lead to sustained high cortisol levels, which can contribute to cognitive impairment in the elderly (31). This stress response can exacerbate the effects of systemic inflammation in the brain. Pro-inflammatory cytokines and prostaglandins are thought to reach brain tissue through structural and functional changes in the blood-brain barrier due to aging. Subsequently, a cascade of events involving endothelial cells, astrocytes, microglia, pericytes, and basal lamina occurs, leading to neuroinflammation processes that result in neuronal injury (32).

In experimental studies on rats, postoperative pain has been reported to promote axon demyelination, decrease neurotrophic factors (BDNF and NG), increase neurodegenerative biomarker expressions (VILIP-1), increase pro-inflammatory factors (TNF-α, IL-1β, IL-6), and decrease anti-inflammatory factors in the hippocampus (33). Adequate analgesia administration can reduce memory dysfunction and overproduction of pro-inflammatory cytokines in the prefrontal cortex and hippocampus (34). Furthermore, neuroinflammatory processes are primarily

detected in the aging hippocampus of rats, which is also associated with the memory dysfunction they experience (35).

Regional anesthesia does not have a greater benefit than GA in reducing the risk of delirium/cognitive impairment post-operatively. The debate about whether regional anesthesia can prevent cognitive impairment after surgery should be brought to a deeper level, considering anesthesia management from preoperative to postoperative. These strategies include preventing hypotension, whether due to spinal anesthesia or bleeding during surgery, managing adequate pain from preoperative to postoperative, avoiding excessive sedation, choosing the type of sedative agent by avoiding midazolam and preferring dexmedetomidine, and selecting analgesia modalities with opioid-sparing strategies.

Our study has several limitations. First, the limited number of studies. Second, the variation in agents and measurement tools. Third, we combined patients undergoing hip replacement and hip fracture surgery. The incidence of POD was reported to be four times lower in patients undergoing hip replacement surgery compared to hip fracture surgery (36).

CONCLUSION

The optimization of perioperative analgesia are beneficial anesthesia strategies to reduce the risk of cognitive impairment in elderly patients undergoing hip surgery with spinal anesthesia.

REFERENCES

1. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Recommendations for the Nomenclature of Cognitive Change Associated With Anaesthesia and Surgery—2018. Anesth Analg. 2018 Nov;127(5):1189–95.
2. Belrose JC, Noppens RR. Anesthesiology and cognitive impairment: a narrative review of current clinical literature. BMC Anesthesiol. 2019 Dec;19(1):241.
3. Kitsis P, Zisimou T, Gkiatas I, Kostas-Agnantis I, Gelalis I, Korompilias A, et al. Postoperative Delirium and Postoperative Cognitive Dysfunction in Patients with Elective Hip or Knee Arthroplasty: A Narrative Review of the Literature. Life. 2022 Feb 20;12(2):314.
4. Zheng X, Tan Y, Gao Y, Liu Z. Comparative efficacy of Neuraxial and general anesthesia for hip fracture surgery: a meta-analysis of randomized clinical trials. BMC Anesthesiol. 2020 Dec;20(1):162.
5. Kendall MC, Cohen AD, Principe-Marrero S, Sidhom P, Apruzzese P, De Oliveira G. Spinal versus general anesthesia for patients undergoing outpatient total knee arthroplasty: a national propensity matched analysis of early postoperative outcomes. BMC Anesthesiol. 2021 Dec;21(1):226.
6. Rong X, Ding Z chuan, Yu H da, Yao SY, Zhou ZK. Risk factors of postoperative delirium in the knee and hip replacement patients: a systematic review and meta-analysis. J Orthop Surg. 2021 Dec;16(1):76.

7. Zhu C, Wang B, Yin J, Xue Q, Gao S, Xing L, et al. Risk factors for postoperative delirium after spinal surgery: a systematic review and meta-analysis. Aging Clin Exp Res. 2020 Aug;32(8):1417–34.
8. Xue P, Wu Z, Wang K, Tu C, Wang X. Incidence and risk factors of postoperative delirium in elderly patients undergoing transurethral resection of prostate: a prospective cohort study. Neuropsychiatr Dis Treat. 2016 Jan;137.
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 May;120(5):999–1008.
10. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343(oct18 2):d5928–d5928.
11. Cochrane Consumers And Communication La Trobe University, Ryan R, Hill S. How to GRADE. 2018;415780 Bytes.
12. Farlinger C, Clarke H, Wong CL. Perioperative pregabalin and delirium following total hip arthroplasty: a post hoc analysis of a double-blind randomized placebo-controlled trial. Can J Anesth Can Anesth. 2018 Nov;65(11):1269–70.
13. Hao J, Dong B, Zhang J, Luo Z. Pre-emptive analgesia with continuous fascia iliaca compartment block reduces postoperative delirium in elderly patients with hip fracture: A randomized controlled trial. Saudi Med J. 2019 Sep;40(9):901–6.
14. Li CX, Ge WC, Yang KN, Zheng HY, Wang XW, Wang YL, et al. [Ultrasound-guided continuous fascia iliaca compartment block for perioperative pain management in elderly patients undergoing hip fracture surgery]. Zhongguo Gu Shang China J Orthop Traumatol. 2023 Nov 25;36(11):1046–51.
15. Monzón DG, Vazquez J, Jauregui JR, Iserson KV. Pain treatment in post-traumatic hip fracture in the elderly: regional block vs. systemic non-steroidal analgesics. Int J Emerg Med. 2010 Dec;3(4):321–5.
16. Sakic L, Tonkovic D, Hrgovic Z, Klasan A. Spinal Dexamethasone Effect on Cognitive Disorders After Hip Surgery. Med Arch. 2023;77(1):18.
17. Tang L, Li B, Guo S, Zhao X, He B, Liu W, et al. Fascia iliaca compartment block can reduce the incidence of early post-operative cognitive impairment in elderly patients with high-risk hip replacement. Front Aging Neurosci. 2022 Dec 5;14:1025545.
18. Xu Z, Tang Z, Yao J, Liang D, Jin F, Liu Y, et al. Comparison of low-dose morphine intrathecal analgesia and sufentanil PCIA in elderly patients with hip fracture undergoing single spinal anesthesia — a randomized clinical trial. BMC Anesthesiol. 2022 Dec;22(1):124.
19. Yamamoto N, Sakura S, Noda T, Nishiyama A, Dan'ura T, Matsui Y, et al. Comparison of the postoperative analgesic efficacies of intravenous acetaminophen and fascia iliaca compartment block in hip fracture surgery: A randomised controlled trial. Injury. 2019 Oct;50(10):1689–93.
20. Zhu M, Mei Y, Zhou R, Wang L, Zhang X. Effects of anterior approach to quadratus lumborum block on postoperative cognitive function following hip surgery in older people: a randomized controlled clinical trial. BMC Geriatr. 2023 Dec 11;23(1):835.
21. Fan Y, Yuan L, Ji M, Yang J, Gao D. The effect of melatonin on early postoperative cognitive decline in elderly patients undergoing hip arthroplasty: A randomized controlled trial. J Clin Anesth. 2017 Jun;39:77–81.
22. Li J zhu, Li X zheng, Wang X min, Wang M shan, Yu H fang, Shi F, et al. [Effects of parecoxib sodium analgesia on serum concentrations of neuron-specific enolase and S-100β and postoperative cognitive function of elderly patients undergoing acute replacement of femoral head]. Zhonghua Yi Xue Za Zhi. 2013 Jul 16;93(27):2152–4.
23. Nuthep L, Klanarong S, Tangwiwat S. The Analgesic effect of adding ultrasound-guided pericapsular nerve group block to suprainguinal fascia iliaca compartment block for hip

fracture surgery: A prospective randomized controlled trial. Medicine (Baltimore). 2023 Nov 3;102(44):e35649.
24. Uysal Aİ. The effect of early femoral nerve block intervention on preoperative pain management and incidence of postoperative delirium geriatric patients undergoing trochanteric femur fracture surgery: a randomized controlled trial. Turk J Trauma Emerg Surg [Internet]. 2019 [cited 2024 Feb 13]; Available from: https://jag.journalagent.com/travma/pdfs/UTD_26_1_109_114.pdf
25. Morrison RS, Magaziner J, Gilbert M, Koval KJ, McLaughlin MA, Orosz G, et al. Relationship Between Pain and Opioid Analgesics on the Development of Delirium Following Hip Fracture. J Gerontol A Biol Sci Med Sci. 2003 Jan 1;58(1):M76–81.
26. Leung JM, Sands LP, Paul S, Joseph T, Kinjo S, Tsai T. Does Postoperative Delirium Limit the Use of Patient-controlled Analgesia in Older Surgical Patients? Anesthesiology. 2009 Sep 1;111(3):625–31.
27. Swart LM, Van Der Zanden V, Spies PE, De Rooij SE, Van Munster BC. The Comparative Risk of Delirium with Different Opioids: A Systematic Review. Drugs Aging. 2017 Jun;34(6):437–43.
28. Zywiel MG, Prabhu A, Perruccio AV, Gandhi R. The Influence of Anesthesia and Pain Management on Cognitive Dysfunction After Joint Arthroplasty: A Systematic Review. Clin Orthop. 2014 May;472(5):1453–66.
29. Singh NP, Makkar JK, Borle A, Singh PM. Role of supplemental regional blocks on postoperative neurocognitive dysfunction after major non-cardiac surgeries: a systematic review and meta-analysis of randomized controlled trials. Reg Anesth Pain Med. 2024 Jan;49(1):49–58.
30. Exsteen OW, Svendsen CN, Rothe C, Lange KHW, Lundstrøm LH. Ultrasound-guided peripheral nerve blocks for preoperative pain management in hip fractures: a systematic review. BMC Anesthesiol. 2022 Dec;22(1):192.
31. MacLullich AMJ, Ferguson KJ, Miller T, De Rooij SEJA, Cunningham C. Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses. J Psychosom Res. 2008 Sep;65(3):229–38.
32. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. Acta Neuropathol (Berl). 2010 Jun;119(6):737–54.
33. Kong E, Geng X, Wu F, Yue W, Sun Y, Feng X. Microglial exosome miR-124-3p in hippocampus alleviates cognitive impairment induced by postoperative pain in elderly mice. J Cell Mol Med. 2024 Feb;28(3):e18090.
34. Koyama T, Kawano T, Iwata H, Aoyama B, Eguchi S, Nishigaki A, et al. Acute postoperative pain exacerbates neuroinflammation and related delirium-like cognitive dysfunction in rats. J Anesth. 2019 Jun;33(3):482–6.
35. Kawano T, Yamanaka D, Aoyama B, Tateiwa H, Shigematsu-Locatelli M, Nishigaki A, et al. Involvement of acute neuroinflammation in postoperative delirium-like cognitive deficits in rats. J Anesth. 2018 Aug;32(4):506–17.
36. Kalisvaart KJ, Vreeswijk R, De Jonghe JFM, Van Der Ploeg T, Van Gool WA, Eikelenboom P. Risk Factors and Prediction of Postoperative Delirium in Elderly Hip-Surgery Patients: Implementation and Validation of a Medical Risk Factor Model. J Am Geriatr Soc. 2006 May;54(5):817–22.

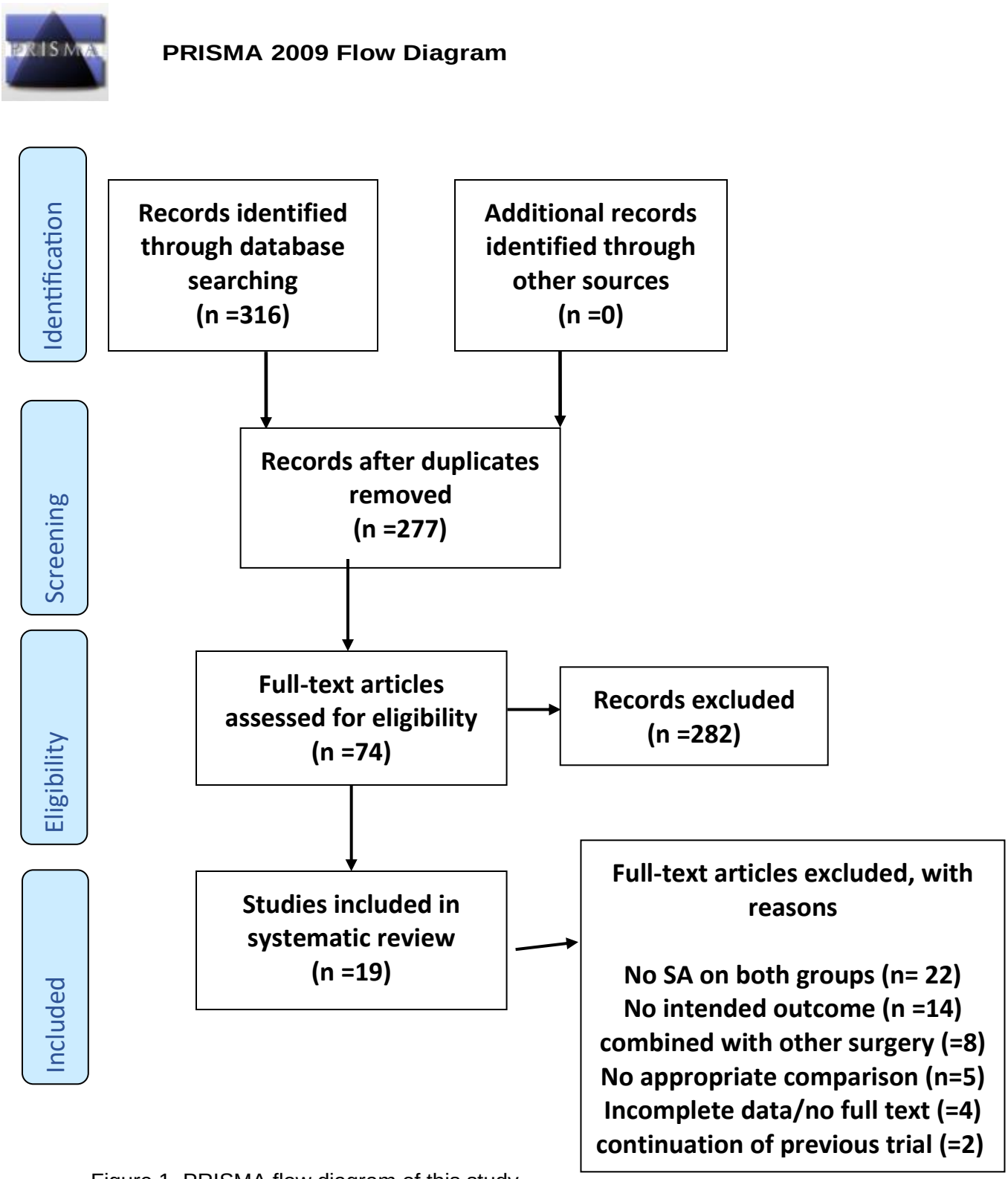

Figure 1. PRISMA flow diagram of this study

Table 1. summary of findings of our meta-analysis

	No of studies	Participants	Effect of estimate	Heterogeneity	GRADE
Pain improvement reduced the risk of delirium?					
POD	6	587	RR 0.37 [0.20, 0.68], $p < 0.05$	I^2= 0%, p=0.65	MODERATE
DNCR at 24h	2	211	RR 0.63 [0.36, 0.91], $p < 0.05$	I^2= 0%, p=0.92	MODERATE
DNCR at 72h	2	211	RR 0.89 [0.08, 1.70], $p < 0.05$	I^2= 87%, $p < 0.05$	LOW
DNCR at 4-7d	2	141	RR 0.30 [-0.04, 0.63], p= 0.08	I^2= 26%, p=0.24	MODERATE