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REVIEW

Regional anesthesia techniques and postoperative delirium: systematic review and meta-analysis

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ABSTRACT

INTRODUCTION: Postoperative delirium is a frequent occurrence in the elderly surgical population. As a comprehensive list of predictive factors remains unknown, an opioid-sparing approach incorporating regional anesthesia techniques has been suggested to decrease its incidence. Due to the lack of conclusive evidence on the topic, we conducted a systematic review and meta-analysis to investigate the potential impact of regional anesthesia and analgesia on postoperative delirium.

EVIDENCE ACQUISITION: PubMed, Embase, and the Cochrane central register of Controlled trials (CENTRAL) databases were searched for randomized trials comparing regional anesthesia or analgesia to systemic treatments in patients having any type of surgery. This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We pooled the results separately for each of these two applications by random effects modelling. Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to evaluate the certainty of evidence and strength of conclusions.

EVIDENCE SYNTHESIS: Eighteen trials (3361 subjects) were included. Using regional techniques for surgical anesthesia failed to reduce the risk of postoperative delirium, with a relative risk (RR) of 1.21 (95% CI: 0.79 to 1.85); P=0.3800. In contrast, regional analgesia reduced the relative risk of perioperative delirium by a RR of 0.53 (95% CI: 0.42 to 0.68; P<0.0001), when compared to systemic analgesia. *Post-hoc* subgroup analysis for hip fracture surgery yielded similar findings.

CONCLUSIONS: These results show that postoperative delirium may be decreased when regional techniques are used in the postoperative period as an analgesic strategy. Intraoperative regional anesthesia alone may not decrease postoperative delirium since there are other factors that may influence this outcome.

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KEY WORDS: Conduction anesthesia; Postoperative complications; Delirium; Perioperative care.

Introduction

Postoperative delirium (POD) is defined as a condition encompassing altered mental status and acute attention disorders that in most cases occurs within five days of surgery.[1] The incidence of POD is 20% to 45% among older adult surgery patients.[2] The frailty of the patient, as well as preexisting cognitive impairment, may predispose to the development of this complication. The use of opioids and hypnotic drugs, surgical stress, pain, and a reduction in mobility have also been reported to be factors involved in the pathogenesis of this type of complication.

Regional anesthetic techniques and other opioid-sparing approaches have been suggested to prevent POD in published European guidelines, although this recommendation is supported by a low quality of evidence.[3]

It is unclear whether or not the timing of the regional anesthetic intervention has an influence on POD. While regional anesthesia use intraoperatively may avoid unnecessary opioids and other sedatives during surgery, there may be a greater beneficial effect on POD if regional anesthetic techniques are extended further into the postoperative period. In theory, regional anesthesia may offer additional advantages in terms of earlier return of bowel function, reduced incidence of pulmonary dysfunction, and reduced inflammatory response to surgery that may have influence on cognitive function.[4]

This systematic review and meta-analysis build on the previously published guidelines from 2017 with an updated evidence review to investigate the risk of POD throughout the perioperative period and evaluate the potential influence of regional anesthesia and analgesia. Thus, we designed this study to consider two different perioperative interventions: 1) anesthesia, comparing regional anesthesia to general anesthesia; and 2) analgesia (pre- and postoperative), comparing regional analgesia to systemic analgesia.

Evidence acquisition

Data sources

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[5] The Cochrane Handbook for Systematic Reviews of Intervention was chosen as the methodological guidance.[6]

The protocol was registered prospectively in PROSPERO (CRD42021253590).

The following databases were used: PubMed, Embase, and the Cochrane central register of Controlled trials (CENTRAL). Searches were conducted for studies published up to 11th May 2021. Only randomized clinical trial (RCT) articles published in English and Italian were eligible for inclusion.

In addition, potentially relevant studies were searched in ClinicalTrials.gov, reference lists of

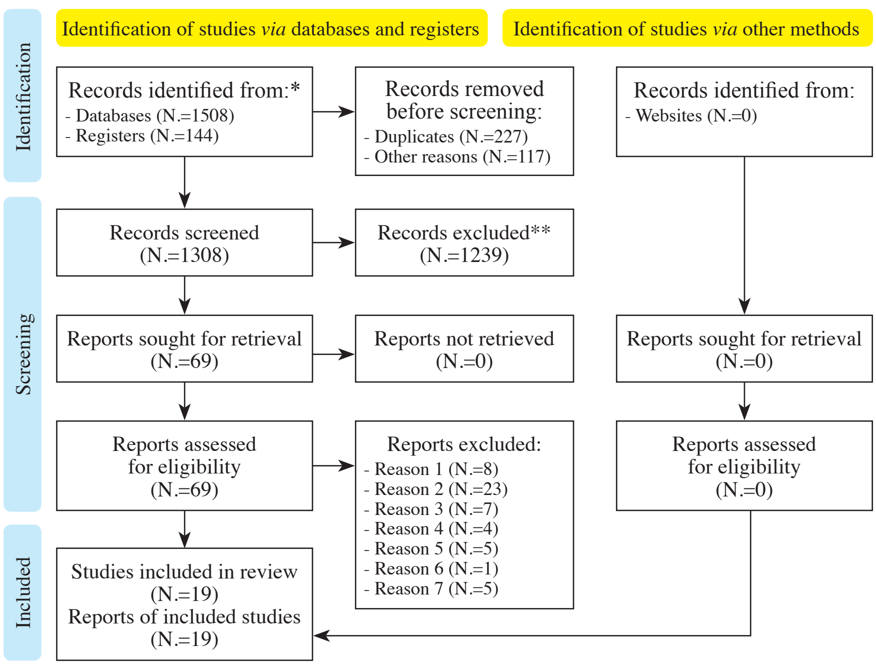

Figure 1.—PRISMA diagram of studies included in this review.[7]
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers); **if automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

included articles, and the grey literature sources (*i.e.*, opengrey.eu, greylit.org) (Figure 1).[7] Specific search strategies were created for each database (Supplementary Digital Material 1: Supplementary Table I).

Population

The search was limited only to RCTs with participants meeting the following inclusion criteria: adults (>18 years old) of any gender undergoing surgery by comparing the effect of regional anesthesia to general anesthesia or systemic treatment by evaluating the occurrence of POD, evaluated with approved tools such as CAM, DSM-IV criteria, up to seven days after surgery.

The population was then divided into the following groups:

- regional anesthesia versus general anesthesia (anesthesia);
- regional analgesia versus systemic analgesia (analgesia).

Intervention and comparator

RCTs comparing regional anesthesia (spinal anesthesia or epidural anesthesia) versus general anesthesia in the anesthesia setting and regional analgesia (peripheral nerve blocks and fascial blocks) versus systemic analgesia (including placebo with 0.9% saline) in the analgesia setting with patients undergoing any type of surgery.

Given the complexity of the geriatric hip fracture population compared to elective surgical patients, this subgroup was analyzed separately.[8]

To minimize bias, we repeated the meta-analysis by including only studies that utilized preoperative delirium in the exclusion criteria.

Outcomes

The main outcome of interest was the presence of POD during the postoperative period. The presence of the outcome was reported by the authors as a dichotomous variable, based on clinical assessment and validated questionnaires to detect POD.

Data extraction and quality assessment

Search results were exported to EndNote V.X9 (Clarivate Analytics, PA, USA). Duplicates were automatically removed. The review process was carried out in two steps consisting of: 1) title and abstract review process; 2) full text review process. For both levels, two authors (A.F. and E.B.) independently screened the articles with conflicts resolved by a third author (F.A.).

A planned Excel spreadsheet was used to extract data (patient characteristics, type of surgery, follow-up periods, outcome measures and main results). The authors of any ongoing studies were contacted to include unpublished data if applicable.

Risk of bias assessment

Two authors (A.F. and E.B.) independently assessed the risk of bias through the Revised Cochrane risk-of-bias tool for RCTs (RoB 2), five with conflicts resolved by a third author (F.A.). A risk of bias graph was created by RobVis visualization tool (Figure 2).[4, 9-26] To assess the quality of evidence for the primary outcome, the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used, classifying evidence as high, moder-

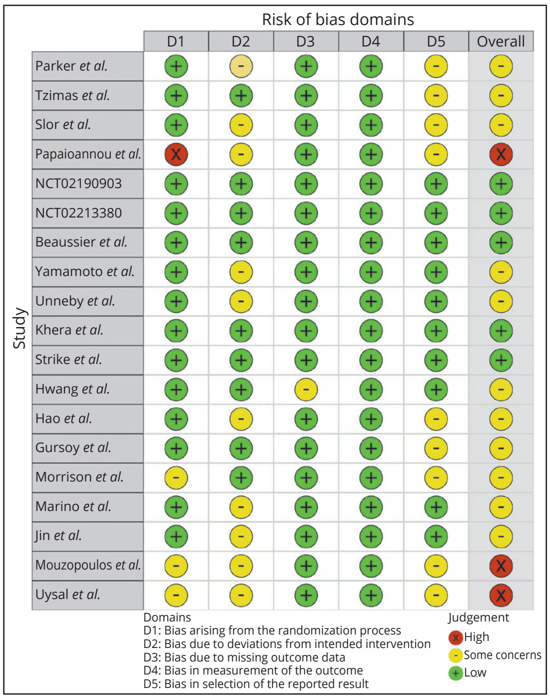

Figure 2.—Risk of bias summary (RobVis visualization tool).[4, 9-25]

ate, low, or very low quality based on considerations of risk of bias, directness, precision, and publication bias.[27] We used GRADEpro GDT[28] to generate the GRADE summary of findings table.

Statistical analysis

For dichotomous outcomes, the risk ratio (RR) and corresponding 95% confidence interval (CI) were calculated. Statistical heterogeneity was determined with the I^2. Heterogeneity was assessed using the I^2 index, with values of 25%, 50%, and 75%, taken to indicate low, moderate, and high levels of heterogeneity, respectively.[6] We considered the following as sources of heterogeneity: differences in the treatment, the treated population, the study design, or the data analysis method. The Mantel-Haenszel and random effects model were chosen for the meta-analysis of the outcome.

Effectiveness was judged based on statistical significance. Statistical significance was based on whether or not the 95% CI included 1.

Publication bias was assessed when more than ten studies were available in the analysis.[29] Data were analyzed with Review Manager (Revman) software.[30]

Evidence synthesis

Search output

The systematic literature search performed on 11th May 2021 retrieved 1508 results in databases and 144 in registers. After deduplication, abstracts of 1308 studies were evaluated leading to 1239 studies being excluded and 69 studies being selected for full-text evaluation. Among the remaining 69 studies, eight were excluded because the analgesic technique was not compatible with those chosen for our population, 22 were excluded because the full-text had never been published and neither had data available, eight were excluded for not being randomized trials, four were excluded because they did not report a dichotomous outcome but an average of scores performed on testing, four were ongoing clinical trials for which we did not received a response to the request for preliminary data, one was excluded because it reported outcomes after three months, and four were excluded because postoperative cognitive dysfunction was reported as the main outcome. A list of excluded studies is provided in Supplementary Digital Material 2 (Supplementary Table II). Finally, eighteen studies were considered for the systematic review and meta-analysis: six anesthesia and 12 analgesia, respectively.

As several studies had a high risk of bias, we conducted a sensitivity analysis excluding them. The result of the meta-analysis did not change.

A flow chart describing the complete literature search process is reported in Figure 1.

Anesthesia

All six studies[9-12] and NCT02190903, NCT02213380 investigated POD in patients undergoing surgery who received regional anesthesia intraoperatively (Supplementary Digital Material 3: Supplementary Table III). Pooled results did not show a statistically significant difference (RR=1.21 [95% CI 0.79 to 1.85]; P=0.38, I^2=22%, χ^2=6.43, df=5) (Figure 3). The certainty of evidence was low (Table I).

Analgesia

All twelve RCTs[13-24] investigated POD in patients undergoing surgery who received regional analgesia before or after surgery (Supplementary Table III). Pooled results showed a statistically significant difference favoring regional analgesia (RR=0.53 [95% CI 0.42 to 0.68]; P<0.0001, I^2=1%, χ^2=9.78, df=10) (Figure 4). The certainty of evidence was low (Table II).

Hip fracture surgery subgroup analysis

Anesthesia

All five studies[10-12] and NCT02190903, NCT02213380 investigated POD in patients undergoing surgery who received regional anesthesia intraoperatively (Supplementary Table III). Pooled results showed no difference (RR=1.19 [95% CI 0.71 to 2.00], P=0.50, I^2=35%, χ^2=6.17, df=4) (Figure 3). The certainty of evidence was very low (Table I).

Analgesia

All six studies[14, 17, 18, 20, 22, 23] investigated POD in patients undergoing surgery who received regional analgesia before or after surgery (Supple-

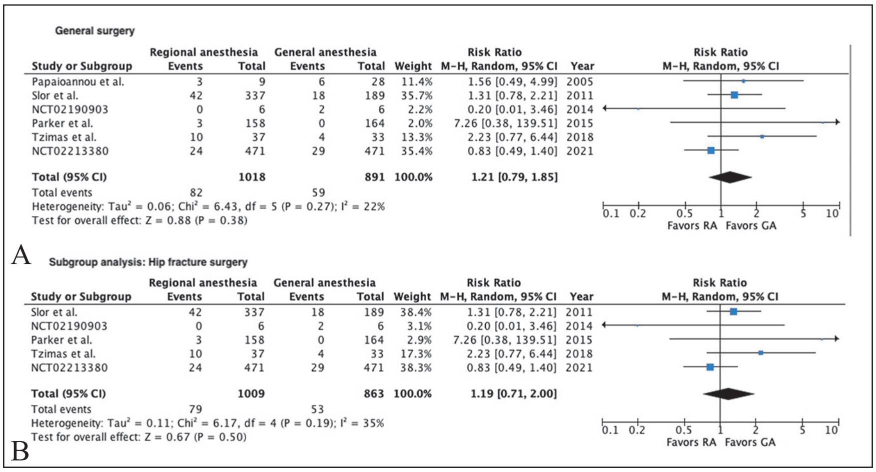

Figure 3.—Forest plot for regional analgesia compared to general anesthesia for postoperative delirium. Values presented as mean difference with 95% confidence intervals.[9-12]

Table I.—*Summary of findings, regional analgesia compared to general anesthesia for postoperative delirium.*

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	N. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with general anesthesia	Risk with regional anesthesia				
Delirium risk in major surgery	7 per 100	8 per 100 (5 to 12)	RR 1.21 (0.79 to 1.85)	1909 (6 RCTs)	⊕⊖⊖⊖ Very low [a, b, c]	Regional anesthesia may result in little to no difference in delirium risk
Delirium risk in hip fracture surgery	6 per 100	7 per 100 (4 to 12)	RR 1.19 (0.71 to 2.00)	1872 (5 RCTs)	⊕⊕⊖⊖ Low [a, c]	Regional analgesia may reduce delirium risk *vs.* systemic analgesia slightly

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio; GRADE: Working Group grades of evidence; high certainty: we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
[a] Downgrade because studies have a high risk of bias; [b] downgrade by one level because studies use selection criteria that are difficult to apply; [c] downgrade by one level because confidence intervals are generally wide.

mentary Table III). Pooled results showed a statistically significant difference (RR=0.58 [95% CI 0.44 to 0.76], P=0.0001, I^2=0%, χ^2=2.77, df=5) (Figure 4). The certainty of evidence was very low (Table II).

Subgroup analysis including only patients without preoperative delirium

Anesthesia

All five studies[9, 10, 12] and NCT02190903, investigated POD in patients without preoperative delirium or alterations in consciousness undergoing surgery who received regional anesthesia intraoperatively. Pooled results showed no difference (RR=1.26 [95% CI 0.75 to 2.12], P=0.38, I^2=13%, χ^2=3.43, df=3.43).

Analgesia

All nine studies investigated POD in patients without preoperative delirium or alterations in consciousness undergoing surgery who received regional analgesia before or after surgery (Supplementary Table III). Pooled results showed a statistically significant difference (RR=0.49 [95% CI 0.35 to 0.69], P=0.0001, I^2=12%, χ^2=9, df=8) (Figure 4). The certainty of evidence was low (Table II).

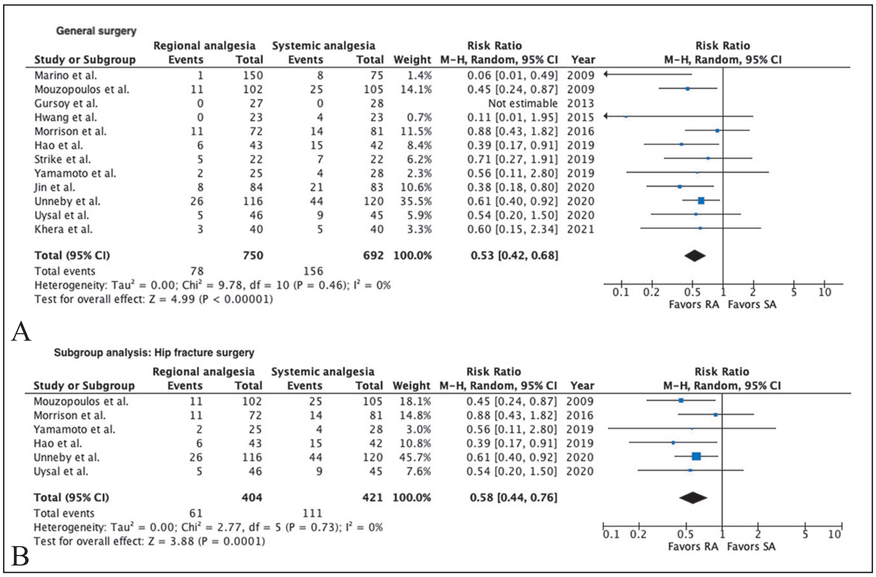

Figure 4.—Forest plot for regional analgesia compared to systemic analgesia for postoperative delirium. Values presented as mean difference with 95% confidence intervals.[14, 17, 18, 20, 22, 23]

Table II.—*Summary of findings, regional analgesia compared to systemic analgesia for postoperative delirium.*

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	N. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with systemic analgesia	Risk with regional analgesia				
Delirium risk in major surgery	23 per 100	12 per 100 (9 to 15)	RR 0.53 (0.42 to 0.68)	1442 (12 RCTs)	⊕⊕⊖⊖ Low [a, c]	Regional analgesia may reduce delirium risk *vs.* systemic analgesia slightly
Delirium risk in hip fracture surgery	26 per 100	15 per 100 (12 to 20)	RR 0.58 (0.44 to 0.76)	825 (6 RCTs)	⊕⊖⊖⊖ Very low [a, b, c, d]	The evidence is very uncertain about the effect of regional anesthesia on postoperative delirium reduction
Delirium risk in major surgery*	21 per 100	10 per 100 (7 to 15)	RR 0.49 (0.35 to 0.69)	1071 (9 RCTs)	⊕⊕⊖⊖ Low	RA may reduce delirium risk in major surgery* slightly

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; RR: risk ratio; GRADE: Working Group grades of evidence; high certainty: we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
[a] Downgrade because studies have a high risk of bias; [b] downgrade by one level because studies use selection criteria that are difficult to apply; [c] downgrade by one level because confidence intervals are generally wide; [d] too few studies to determine this, and results with extremely heterogeneous confidence intervals.
* Population selected with preoperative delirium as an exclusion criterion.

Discussion

The results of this updated systematic review and meta-analysis support the use of regional analgesia over systemic analgesia in the postoperative period based on a decreased associated risk of POD. However, intraoperative regional anesthesia is not associated with decreased incidence of POD. These findings are unrelated to the type of surgery and are consistent in the hip fracture surgery subgroup and subgroup of patients without preoperative delirium. Our findings support recommendations stated in the European guidelines about using regional analgesia to decrease opioid exposure and the risk of POD[3] A meta-analysis conducted in 2018 by Patel *et al*., including both RCTs and non-RCTs is in agreement with our results, comparing RA with GA.[31] Thus, considering the new publications, there are no new findings regarding the development of POD with respect to the selected anesthesia technique.[32]

Although the use of regional anesthesia, thereby avoiding general anesthesia, may not have an effect on POD when limited to the intraoperative period, previous studies have demonstrated the benefits of neuraxial anesthesia on other complications especially in the context of frail patients.[31, 33] The results of our study may have been affected by both the high risk of bias in the individual studies and the paucity of the studies included, and the publication of future studies may necessitate an updated systematic review and meta-analysis. The feasibility of using neuraxial anesthesia as the intraoperative anesthetic technique is limited to particular surgical settings, and this lack of broad generalizability should be considered when interpreting our results.

As a planned subanalysis, we evaluated the hip fracture surgery population separately since these patients tend to be older and frail. Regional analgesia in the form of nerve blocks has been shown to reduce opioid consumption after major hip surgeries,[34] and other sedating medications are known contributors to the development of POD, especially in the elderly.[35] Our results confirm the findings of a recent Cochrane review, in which the use of regional analgesia in the form of peripheral nerve blocks in patients undergoing hip fracture surgery has an impact on POD development.[32] However, this review does not specifically discuss POD, giving only a few suggestions, and addressing other main outcomes such as pain and immediate postoperative complications. Furthermore, the implementation of regional analgesia remains heterogeneous with variations existing in technique, medication administration, use of continuous catheters versus single-injection, and timing of the block either before or after surgery; these factors, individually or in combination, may have an impact on the onset of POD and may not be easily standardized since many variables contribute to making each hip fracture case unique. However, robust evidence is still lacking in this aera.[17, 36]

In another subanalysis, we excluded studies that did not screen patients for preoperative delirium. This resulted in a greater positive effect associated with regional analgesia continuation in the postoperative period and a lower degree of heterogeneity in the included studies. The results for regional anesthesia (intraoperative only) did not differ from the main analysis. In clinical practice, proper patient selection is critical when considering anesthetic and analgesic techniques, and the presence of preoperative delirium or any level of altered consciousness should influence perioperative management.

The present study adds to the scientific literature as it is the only meta-analysis to date which examines the utilization of regional anesthesia or analgesia during specific time intervals and identifies the differential effect on risk of POD. A prior meta-analysis evaluated potential risk factors for POD in patients undergoing vascular surgery but included only three RCTs involving regional analgesia, and no evidence was found.[37] A recent meta-analysis by Wu *et al.* showed that regional anesthesia is a predisposing factor for the risk of POD in patients undergoing hip fracture surgery.[38] This conclusion is based only on five non-RCT publications.

The most important limitation of this meta-analysis is the high risk of bias in the studies considered. Another relevant limitation of this analysis was the clinical heterogeneity underlying the studies.

We are also unable to say — because a direct comparison is lacking in the literature — whether regional analgesia maintains the benefit on POD when compared with other opioid-sparing analgesic techniques. Any mechanism specific to regional anesthesia techniques that may lead to a decrease in POD remains speculative and may include early mobility and prevention of complications related to pain and opioid consumption. It is not possible to determine causality, in this type of study. However, other drugs involved in opioid-sparing analgesic protocols such as ketamine and gabapentin, have not been shown to affect the development of POD.[39, 40]

The regional analgesia groups were subject to differences in practice such as the timing of the block, the choice between a continuous peripheral block or a single injection block, and the type of surgery (Supplementary Table III). Femur fracture repair procedures are amenable to a wide variety of analgesic procedures as well as timing of these interventions.

Conclusions

Based on this updated systematic review and meta-analysis, we can conclude that regional analgesia may reduce the incidence of POD in patients undergoing various types of surgery. Further high quality RCTs should be performed defining the type and timing of peripheral blocks used. Validated POD tests should consistently be used to improve study quality. Regarding the intraoperative management, insufficient data are available to support regional anesthesia rather than general anesthesia purely for the prevention of POD, but other benefits of neuraxial anesthesia have been described. The choice of anesthetic technique remains a shared decision between patients and their physicians.

Key messages

- Postoperative delirium (POD) continues to be a poorly understood and multifactorial adverse outcome.
- Intraoperative regional anesthesia alone does not seem to affect the incidence of POD.
- Applying regional analgesia in the postoperative period may reduce the incidence of POD in patients undergoing various types of surgery.

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