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Postoperative Delirium with Intravenous Patient-controlled Analgesia (IVPCA) Compared with Regional Analgesia for General Anesthesia: Systematic Review and Meta-analysis

Majid Vatankhah[1], Mohammad Sadegh Sanie Jahromi[2], Mansoor Deilami[3], Mojtaba Ghaedi[2], Hassan Zabetian[2], Somayeh Mehrpour[4], Samaneh Abiri[5], Lohrasb Taheri[6], Bibi Mona Razavi[1], Samira Zanbagh[1], Navid Kalani[7] and Pourya Adibi[1*]

[1] Anesthesiology, Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
[2] Research Center for Noncommunicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran
[3] Department of Anesthesiology and Critical Care, 5 Azar Hospital, Golestan University of Medical Sciences, Golestan, Iran
[4] Department of Anesthesiology, Shahid Beheshti Hospital, Qom University of Medical sciences, Qom, Iran
[5] Department of Emergency Medicine, Jahrom University of Medical Sciences, Jahrom, Iran
[6] Department of Surgery, Jahrom University of Medical Sciences, Jahrom, Iran
[7] Research Center for Social Determinants of Health, Jahrom University of Medical Sciences, Jahrom, Iran

*** *Corresponding author:*** Pourya Adibi, Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran. Email: adibip@hums.ac.ir

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Abstract

Background: Although the use of systemic narcotics has been established as the gold standard in pain control after surgery, the literature shows the possibility of a higher incidence of delirium after systemic administration of analgesics compared to regional methods, such as epidural and paravertebral analgesia.

Objectives: To compare the rate of postoperative delirium when treated with systemic intravenous patient-controlled analgesia (IVPCA) with regional analgesia methods (continuous or patient-controlled).

Methods: We searched PubMed, Web of Science, Embase, and Scopus databases for relevant papers reporting delirium after surgery based on the regional analgesia methods compared with systemic IV analgesia. Risk ratios for delirium were pooled using a random effects model.

Results: 6 randomized clinical trials (RCT) with a total of 898 cases were selected in which delirium was observed 2 to 7 days after the operation. In a random-effect model of the risk ratio of delirium in patients receiving IVPCA versus patients receiving regional PCA, with 487 and 486 participants in each arm, there was a retrospective1.85 -fold higher risk of delirium with a 95% confidence interval of 1.35 to 2.53 compared with regional methods of analgesia (I2=0%; low heterogenicity). Although we attempted a comprehensive review of the literature, publication bias occurred, so we imputed the missing studies to the literature by the trim-and-fill method, which forced us to imput the missed studies of the literature by trim and fill method that showed the similar adjusted results of RR=1.75, 95% CI: 1.29 to 2.39. The RCTs assessed had relatively low quality evidence.

Conclusion: There appears to be a large difference in delirium risk between the methods compared, with blinded trials with larger sample sizes required Safety and cost-benefit aspects should also be considered before the clinical application of these results.

Keywords: Epidural analgesia, Patient-controlled analgesia, Paravertebral analgesia, Postoperative delirium

1. Background

Delirium is a severe and fluctuating change in the patient's mental state associated with reduced alertness and impaired attention. Postoperative delirium begins upon awakening and occurs several days after the operation (1). Postoperative delirium is one of the side effects after surgery that can occur in all age groups, from children to the elderly. The risk factors for postoperative delirium are divided into three groups: before surgery, during surgery and after surgery (2). Elderly people are more prone to delirium as they are more likely to have risk factors, such as cognitive impairment, comorbidities, and sensory deficits, malnutrition, use of multiple medications, and impaired functional status. In addition, delirium is common in all age groups when risk factors such as major surgery or emergency surgery are present (3). Every year, more than 2.3 million older people experience delirium during hospitalization. This disorder causes more than 17.5 million days of hospitalization and costs four to seven billion dollars in medical care (4). The prevalence of delirium is 1% in the general population, 10% in the emergency department and about 50% in hospitalized patients (5). The incidence of delirium has been reported to be 1 to 3% after cataract surgery, 73.5% after orthopedic and open heart surgery (5) and 90% after thoracotomy (6). Delirium is frequently observed in the recovery room and is a predictor of postoperative delirium on the ward. Therefore, delirium after surgery on the ward is detected by monitoring (7). Timely diagnosis and treatment of delirium is an essential factor in reducing the duration and intensity of delirium and its negative consequences (side effects) (8). Therefore, it is important to know the predictors of delirium after surgery so that patients prone to

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delirium after surgery can be identified. Measures can then be taken to prevent these complications (9). Postoperative cognitive dysfunction (POCD) is a new onset of cognitive impairment that may persist for weeks or months after surgery (8,9). In 1968, the concept of controlled analgesia was introduced to patients by using an intravenous injection of morphine to measure the degree of analgesia. The first controlled analgesia device for patients was produced in 1971 (10). This device is used for postoperative pain control. Today, PCA can be accessed in many other ways. Extensive studies on the use of PCA have demonstrated the safety and reliability of the device. Through PCA, patients receive medication, when needed, leading to a reduction in anxiety and stress, which are the main factors for pain after surgery (10). Epidural patient-controlled analgesia (PCEA) has become widespread worldwide in recent decades and, together with systemic analgesia procedures, can provide acceptable analgesia for patients (11,12). Another method is paravertebral blockade, which is also widely used in abdominal surgery, particularly in outpatient inguinal hernia repair for anesthesia and analgesia. Compared to spinal techniques, this block prevents severe autonomic dysfunction and allows the patient to be discharged earlier (13,14).

2. Objectives

However, there is no study comparing the incidence of postoperative delirium with systemic and epidural or regional analgesia techniques.

3. Methods

This is a PRISMA-based systematic review and meta-analysis of the literature. We searched PubMed, Web of Science, Embase, Clinicaltrails.gov, and Scopus databases for relevant papers reporting delirium after surgery based on regional analgesia methods compared with systemic IV analgesia. We searched for articles with a prospective clinical trial design to be included in the analysis. The year of publication of the article was not restricted. Studies comparing two regional analgesic methods were not included. The search approach included all conceivable combinations of the keywords of the ”delirium”, “confusion”, “ postoperative cognitive dysfunction”, “Postoperative delirium” and “patient controlled analgesia”, “continuous analgesia”, “continuous IV analgesia”, “continuous regional analgesia”, “epidural analgesia”. Studies with non-randomized methods were not included. The selection criteria for inclusion in the study only applied to articles published in English. Gray literature was excluded from the search All search steps were carried out by two independent reviewers. The two researchers first compiled a list of all titles and abstracts of articles that were accessible in the above databases and then assessed each title separately to decide which articles were relevant. In case of disagreement between two researchers, a third reviewer assessed the manuscript. The full texts of the articles were then analyzed for the primary outcome, the occurrence of the delirium. Other variables of study design, setting, type of anesthesia, interventions, type of surgery, mean age of samples, sample size, delirium assessment tool, and follow-up duration were recorded.

The Cochrane Collaboration's risk of bias assessment checklist was used to measure bias in the research (15). Two independent authors assessed the quality of the final papers. In case of disagreement between two researchers, a third reviewer assessed the paper.

3.1. Statistical analysis

Using the Mantel-Haenszel estimation method, the pooled Risk Ratio (RR) for delirium events was estimated based on the RRs of each study in a random-effects model. The I^2 statistic was used to assess heterogeneity. A forest plot was created for the effect size of each study and the combined data with confidence intervals. Egger and Begg tests were used to determine publication bias. In cases where publication bias occurred, the trim-and-fill procedure was used. STATA version 17 was used for all statistical analyses and a p-value of 0.05 was applied.

4. Results

Based on the literature review, an initial search of the four sources considered identified 2378 records. After deleting 740 duplicates, 1638 articles were analyzed for their titles and 1487 irrelevant cases were eliminated. Of the following 77 articles examined on the basis of the article abstract, 74 unrelated articles were eliminated. Finally, the entire texts of 25 articles were analyzed, and 6 RCTs were selected (Figure 1). Clinicaltrails.gov database had 367 related RCTs that only results were published for 28, of which, 15 were selected and only 2 RCTs were aligned with our eligibility criteria (Table S1).

Among the 6 studies evaluated, there were a total of 898 cases observed for 2 to 7 days to assess delirium. Delirium was the primary outcome in the 3 studies with an average of 183 participants, while the other 3 studies with an average of 116 participants in the sample were not suitable for the assessment of delirium (Table 1). The studies used different methods to assess delirium, with the Confusion Assessment Method (CAM), with various extensions to the main instrument, being the most commonly reported. Intravenous patient-controlled analgesia (PCA) was performed with various opioids and tropisetron. Continuous thoracic paravertebral block and thoracic epidural analgesia were performed with

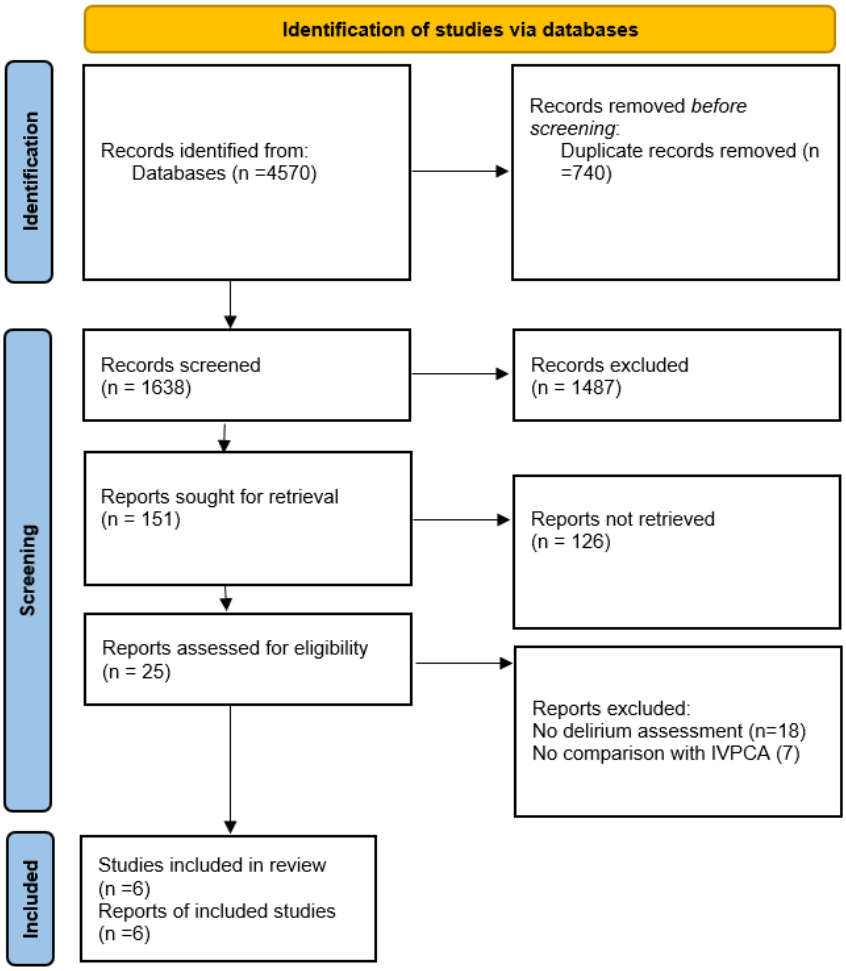

Figure 1. PRISMA flowchart of study selection process

Table 1. characteristics of studies eligible for review

ID	study design	setting	Anesthesia	interventions	surgery	Mean age (IV vs. regional)	sample size	Delirium assessment tool	follow up length
Marino (16)	RCT	USA	GA	IVPCA (hydromorphone) vs. Continuous Lumbar Plexus Block vs. Continuous Femoral Block	unilateral total hip arthroplasty	NR	225	disorientation to time and/or place	2 days
Strike (17)	RCT	2-center (Canada & Latvia)	GA	IVPCA (opioids) vs. continuous thoracic paravertebral block (ropivacaine in Canada and bupivacaine in Latvia)	transcatheter aortic valve replacement	81.7 ± 5.7 vs. 82.3 ± 6.1	44	CAM-ICU	7 days
Jin (18)	RCT	single center, China	GA	IVPCA (Sufentanil and tropisetron) vs. continuous thoracic paravertebral block (ropivacaine and sufentanil)	esophagectomy	71.4 vs. 70.8	167	CAM	4 days
Radovanović (19)	RCT	single center, Serbia	GA	IVPCA (morphine) vs. thoracic epidural analgesia (levobupivacaine, fentanyl and adrenaline)	OPEN COLORECTAL CANCER SURGERY	64.18±9.90 vs. 65.88±10.00	60	CAM	4 days
Wei (20)	RCT	single center, Serbia	GA	IVPCA (sufentanil) vs. thoracic paravertebral block (ropivacaine)	video-assisted thoracoscopic lobectomy	73.5 ± 7.1 vs. 76.2 ± 6.3	338	3D-CAM	7 days
Mann (21)	RCT	single center, France	GA	IVPCA (morphine) vs. thoracic epidural analgesia (bupivacaine and sufentanil)	major abdominal surgery	76.8 ± 4.7 vs. 76.1 ± 5.6	64	DSM 111	5 days

ropivacaine, bupivacaine, sufentanil, levobupivacaine, fentanyl and adrenaline.

In a random-effects model of the risk ratio of delirium in patients receiving IVPCA compared with patients receiving regional PCA (patient-controlled epidural analgesia and thoracic paravertebral block), 6 studies with 487 and 486 participants in each arm were retrospectively analyzed. With low heterogeneity (I^2=0%), there was a 1.85 times greater risk of delirium with 95% confidence interval of 1.35 to 2.53 compared to regional methods of analgesia (Figure 2). Gross evaluation of the funnel plot and Egger and Begg test (P<0.05) revealed asymmetry of the plot, so we applied a trim-and-fill method and assumed that 2 trials were added to the study (Figure 3). This adjustment resulted in a 1.75-fold higher risk of delirium with a 95% confidence interval of 1.29 to 2.39 when comparing PCA with regional methods of analgesia. When the two arms of the Marino et al. (16) (as there were both comparable to IVPCA in case of being regional method) no differences in the pooled RR and heterogeneity or publication bias results.

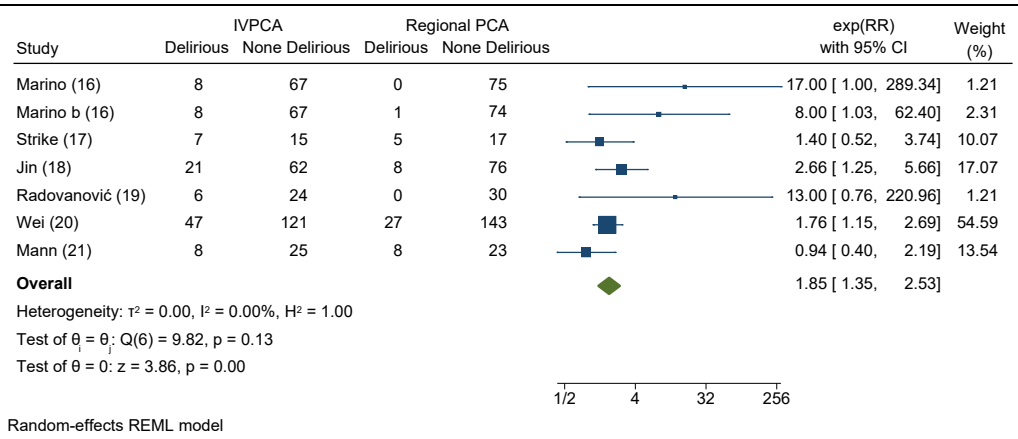

Figure 2. forest plot of the delirium among the IVPCA and regional PCA treatments; Marino b refers the Continuous Femoral Block group. Red line indicates RR of 1

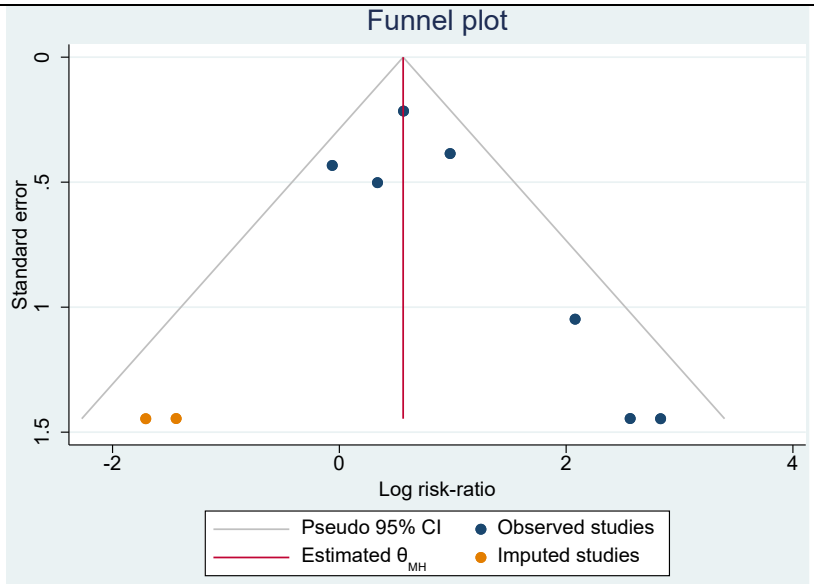

Figure 3. Funnel plot of the delirium among the IVPCA and regional PCA treatments

4.1. Subgroup analyses

Based on the using morphine/hydromorphone and fentanyl, compared to sufentanil in PCA or GA, a subgroup analysis was possible that showed that there was a pooled overall relative risk (RR) of 4.701 (95% CI: 1.176 - 18.794) for studies using Morphine/Hydromorphone and fentanyl. Heterogeneity was not observed with an I2 of 47.50%. Within sufentanil group, which comprised two studies, the overall RR was 1.943 (95% CI: 1.343 - 2.809), and heterogeneity was low with an I2 of 0.00% (Figure 4).

4.2. Risk of bias

The study by Marino et al. (16) had a high risk of bias possibility because the methods of

randomization and concealment were not addressed in the study and the duration of follow-up was only 2 days, and the method of assessing delirium was not standardized. The studies by Strike et al., (17) Jin et al., (18) and Mann et al. did not include information on concealment or blinding of statisticians. The studies by Radovanović et al. and Wei et al. had better information on the methods of the study (Figure 5).

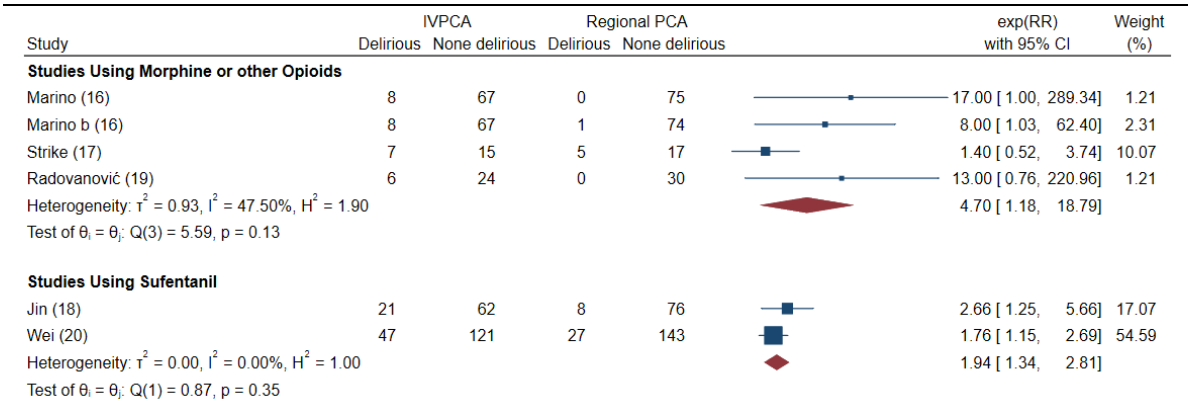

Figure 4. forest plot of the delirium among the IVPCA and regional PCA treatments stratified based on medication type

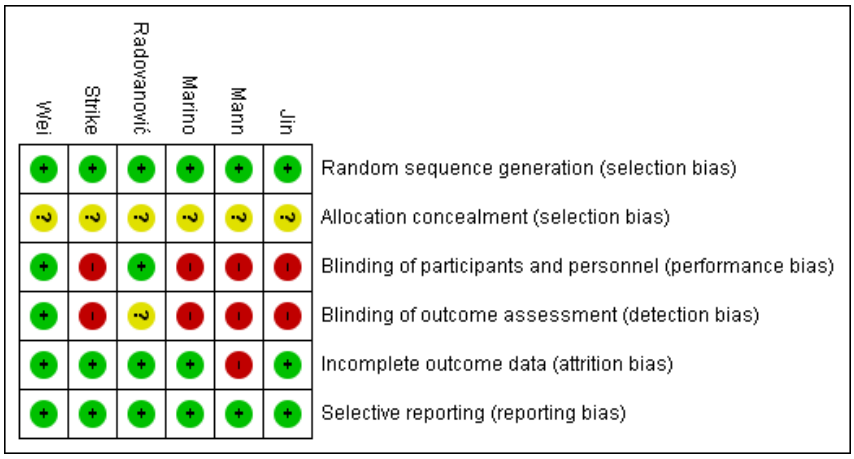

Figure 5. Risk of bias summary; review authors' judgements about each risk of bias item for each included study

5. Discussion

In this review, we found that the risk of delirium was 2.12 (95% CI: 1.56 to 2.88) times higher with IVPCA than with localized analgesia techniques. As far as we are aware, no previous systematic review has examined this question. The most similar study by Fanelli et al. examined the differences in delirium risk between general and regional anesthesia procedures and found a lower risk of delirium with regional anesthesia procedures (22) and Abate et al. drew the same conclusion in noncardiac surgery patients (23); while we evaluated analgesia methods in general anesthesia but our conclusions were similar. A meta-analysis of non-randomized studies by Wu et al. showed that many baseline factors as well as patient condition and type of surgery influence the occurrence of delirium; however, in the aforementioned study, regional anesthesia was associated with higher rates of delirium (24), which is in contrast to the findings of Fanelli et al. However, Wu et al. found 7no publication bias. This could be due to differences in the study design of the studies included in the meta-analyses.

The studies included in our review used different methods to assess delirium, and in some cases the diagnosis of delirium appears to be equivocal. In a systematic review, Bilotta et al. examined the methods used to assess delirium in the postoperative setting and found that validated diagnostic procedures are used less in the literature (25).

Our study was limited due to different types of the surgeries in the reported studies; while we did not saw heterogenicity. One of the limitations of our study had strict eligibility criteria for the inclusion of studies in our systematic review and meta-analysis. The primary rationale behind these stringent criteria was to ensure the selection of homogeneous studies that could be quantitatively merged in the meta-analysis. This might have led some similar studies not to be included in our systematic review, only due to different outcome measures or groupings.

6. Conclusion

In some studies, delirium was not a primary outcome, which may have affected the results when calculating the sample size for RCTs. Although we endeavored to conduct a thorough review of the literature, there existed publication bias. The main purpose of searching sources and databases when conducting systematic reviews is to identify and retrieve all published studies on the topic in question. However, the results of many studies are never published, or only published with a delay, or only presented at conferences. The published studies also tend to overestimate the effectiveness of interventions and underestimate the harms of interventions.

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Footnotes

Conflicts of Interest: There is nothing to declare.
Author's contributions: The systematic review and meta-analysis, led by corresponding author Pourya Adibi, involved a collaborative effort with Majid Vatankhah overseeing conceptualization and methodology development. Contributors like Mohammad Sadegh Sanie Jahromi and Samaneh Abiri played key roles in literature search, data extraction, and statistical analysis. Others, including Mansoor Deilami, Somayeh Mehrpour, and Lohrasb Taheri, contributed to protocol development, quality assessment, and manuscript drafting. The team's comprehensive efforts, guided by Pourya Adibi, ensured a rigorous study, with each author fulfilling crucial roles throughout the research process.
Funding/Support: None.
Ethical statements: This research was a systematic review and meta-analysis and as all information were extracted from existing databases, no ethical concerns arose.

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