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# The effect of non-steroidal anti-inflammatory drugs on postoperative delirium: a meta-analysis

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**Background:** Neuroinflammation is postulated as a potential mechanism underlying postoperative delirium. This study aimed to investigate the impact of non-steroidal anti-inflammatory drug (NSAID) use on postoperative delirium.

**Methods:** We conducted a literature search in electronic databases, including PubMed, EMBASE, CENTRAL, and Web of Science, to identify eligible randomized controlled studies. The primary outcome was the incidence of postoperative delirium, and the secondary outcomes included pain scores and the amounts of opioid used at 24 h postoperatively. We estimated the effect size through calculating the odds ratios (ORs) or mean differences (MDs) with 95% CIs, as appropriate.

**Results:** In the analysis of eight studies involving 1,238 participants, the incidence of postoperative delirium was 11% and 19% in the NSAID and control groups, respectively, with a significant reduction in the NSAID group (OR: 0.54, 95% CI [0.38, 0.7], P = 0.0001, $I^2$ = 0%). NSAID use had a significant effect on postoperative pain reduction (MD: −0.75, 95% CI [−1.37, −0.13], P = 0.0172, $I^2$ = 88%). Significant lower postoperative opioid consumption was observed in the NSAID group (MD: −2.88, 95% CI [−3.54, −2.22], P = 0.0000; $I^2$ = 0%).

**Conclusions:** NSAID administration reduced the incidence of postoperative delirium, severity of pain, and opioid dose used.

**Keywords:** Cognitive dysfunction; Emergence delirium; Neuroinflammation; Neuroinflammatory diseases; Non-steroidal anti-inflammatory agents; Meta-analysis; Pain; Postoperative delirium.

## Introduction

In 2020, the global phenomenon of rapid population aging prompted the World Health Organization and United Nations to designate the period from 2021 to 2030 as the decade of healthy aging, catalyzing campaigns aimed at addressing associated challenges [1,2]. This initiative is particularly pertinent given the burgeoning population of older individuals undergoing surgical interventions, with contemporary medical practice increasingly emphasizing the enhancement of postoperative outcomes in this population. One salient concern in this regard pertains to cognitive function following surgical procedures [3].

Delirium emerges as a pivotal complication in the perioperative period, manifesting at a prevalence of 50%-70% in high-risk patients [4]. The prevention and treatment of delirium are important because they are closely correlated with the prognosis of surgical patients and are linked to long-term cognitive decline [3]. Causative investigations, such as those undertaken in the Successful Aging after Elective Surgery (SAGES) I and II studies,

highlight neuroinflammation as a pivotal element of this phenomenon but have yet to establish definitive mechanisms behind it [5,6].

Putative mechanisms underlying postoperative delirium include perioperative inflammatory responses that could induce neuroinflammation [7]. Non-steroidal anti-inflammatory drugs (NSAIDs), as representative medicines with anti- inflammatory effects, are widely used for pain control in surgical patients. A retrospective analysis exploring the correlation between NSAIDs and the occurrence of delirium, as well as mortality rates, demonstrated a 24% reduction in delirium occurrence and lower one-year mortality with NSAID use [8]. However, the effect of NSAIDs on postoperative delirium remains a subject of conflicting evidence from randomized controlled trials (RCTs) [9,10].

Based on the hypothesis that NSAIDs could potentially lower the incidence of postoperative delirium, this meta-analysis aimed to investigate the effect of NSAID use on the occurrence of postoperative delirium.

## Materials and Methods

This meta-analysis adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [11]. The study protocol was preregistered with the International Prospective Register of Systematic Reviews (identifier: CRD42023487861).

### Eligibility criteria

The inclusion criteria were determined based on the following PICOS (population, intervention, comparison, outcomes, and study design): (P) patients who underwent surgery, (I) perioperative administration of NSAIDs or aspirin, (C) use of placebo or no drugs, (O) assessment of postoperative delirium incidence, and (S) human studies including RCTs. Exclusion criteria encompassed studies lacking control groups, observational or retrospective studies, narrative and review articles, protocols, and articles solely in an abstract form.

### Search strategy

We conducted a comprehensive search for eligible trials across electronic databases, including PubMed, EMBASE, CENTRAL, and Web of Science, spanning from their inception to October 4, 2023, without imposing limitations based on publication year, journal, region, or language. The search terms utilized comprised 'NSAID,' 'aspirin,' and 'postoperative delirium.' The detailed search strategy is available in Supplementary Table 1.

### Study selection

Two independent assessors (SYK, HJS) applied the eligibility criteria to select the studies. The non-English article was translated using Google Translate [12]. A preliminary screening based on the title and abstract was conducted to identify pertinent studies, followed by a comprehensive review of the full texts to finalize the selection of eligible studies. In cases of discrepancy between the two assessors, a third evaluator (HSN) intervened to resolve any differences through discussion.

### Data extraction

Following the conclusive selection of RCTs based on full-text examination, the following variables were extracted: authors, publication year, number of participants, types of surgical procedures, types of NSAIDs, postoperative delirium incidence, postoperative pain score, and administered rescue analgesics. When continuous data were initially presented as medians with interquartile ranges, they were converted into means and standard deviations using Wan's formula [13]. The data depicted in the graphs was obtained by extracting values from the images using WebPlotDigitizer, a tool available at https://apps.automeris.io/wpd/.

### Assessment of the risk of bias

Two authors (SYK, HJS) conducted an independent assessment of the risk of bias using the Cochrane risk-of-bias tool for randomized trials 2 (RoB 2) [14]. The tool encompassed six predefined categories: randomization, deviations from the intended interventions, missing outcome data, outcome measurement, selection of reported results, and other potential biases. The risk of bias was categorized as 'low risk,' 'some concerns,' or 'high risk' within each of these domains. The results of the risk of bias assessment were visualized using the Risk Of Bias Visualization tool (ROBVIS) tool.

### Outcome measures

The primary outcome measure focused on the incidence of postoperative delirium. Secondary outcomes encompassed pain scores and total amounts of opioids used at 24 h after surgery. Various types of opioids were used in the analyzed studies, including morphine [15], sufentanil [10], and hydromorphone [16]. To synthesize the data, we converted the amounts of opioids to mor-

phine-equivalent doses using an equianalgesic dosage conversion calculator (Clincalc.com/Opioids/).

### Certainty of evidence

The certainty of evidence for each outcome was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [17] that considers five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

### Statistical analysis

The analysis of the data utilized Stata SE™, version 17 (Stata Corp.). Dichotomous variables were analyzed using the odds ratio (OR), whereas continuous variables were assessed using the mean difference (MD). A random-effects model was chosen due to the variability in treatment effects across trials.

A sensitivity analysis was conducted using the leave-one-out method to gauge the impact of individual studies on the overall outcomes. Assessment of heterogeneity relied on Cochran's Q test and $I^2$ statistics, categorizing heterogeneity as high ($I^2$ = 76%–100%), moderate ($I^2$ = 26%–75%), or low ($I^2$ = 0%–25%). Publication bias assessment was performed using funnel plots. However, caution is required in the interpretation due to the limited number of included studies (< 10 trials). Statistical significance was established at $P < 0.05$.

## Results

### Study selection

A total of 1,293 articles were identified from electronic databases: PubMed (n = 91), EMBASE (n = 1,014), Cochrane (n = 133), and Web of Science (n = 55). After removing 50 duplicate studies, 1,214 articles were excluded based on the title and abstract. After excluding thirteen studies for which the full manuscripts could not be retrieve, the full texts of the remaining 16 articles were thoroughly reviewed, leading to the selection of eight RCTs for the final analysis (Fig. 1).

The demographics of each included study are described in Table 1. In total, 1,238 patients were included in the final analysis. Five studies used parecoxib [9,15,18–20], two studies used flurbiprofen [10,21], and the other study used diclofenac [16]. There were no RCTs that examined the effect of aspirin on the occurrence of delirium after surgery. In seven studies [9,10,15,18–21], participants' mean age ranged from late sixties to early seventies, encompassing predominantly older individuals. However, one study [16] targeted a comparatively younger population, with a mean age in the thirties. Four studies [9,10,20,21] used the Confusion Assessment Method (CAM) as the measure for assessing postoperative delirium, while another study [19] employed the Mini-Mental State Examination (MMSE). Mu et al. [15] combined the use of the CAM with the MMSE for evaluation. In a study by Hala et al. [18], an internally developed scoring system was employed. This scoring system assessed delirium on a scale of 1 to 5, where 1 indicated the presence of anxiety, 2 denoted disorientation, 3 marked memory failure or motor restlessness, 4 represented uncooperative behavior, and 5 denoted a threatening demeanor. Zeiner et al. [16] utilized a delirium detection score validated by Otter et al. [22] in their research.

### Incidence of postoperative delirium

Eight studies [9,10,15,16,18–21] with 1,238 participants were included. The incidence of postoperative delirium was 11% (68/616) and 19% (118/622) in the NSAID and control groups, respectively. The incidence of postoperative delirium was decreased in the NSAID group compared with the control group (OR: 0.54, 95% CI [0.38, 0.76], P = 0.0001, $I^2$ = 0%; Fig. 2).

Subgroup analysis showed that NSAIDs significantly reduced the incidence of postoperative delirium compared with control in both subgroups, 'general anesthesia' (five studies [9,10,16,18,21]; OR: 0.60, 95% CI [0.37, 0.98], P = 0.0416, $I^2$ = 0%; Fig. 2) and 'regional anesthesia' (two studies [15,19]; OR: 0.48, 95% CI [0.29, 0.79], P = 0.0037, $I^2$ = 0%; Fig. 2). No publication bias was confirmed based on the symmetrical funnel plot (Supplementary Fig. 1). The pooled effect size remained consistent in the sensitivity analysis, supporting the robustness of our results (Supplementary Fig. 2).

### Severity of postoperative pain

Five studies [9,10,15,16,20] with a total of 952 participants were included in this analysis. The use of NSAIDs contributed to a reduction in postoperative pain MD: −0.75, 95% CI [−1.37, −0.13], P = 0.0172, $I^2$ = 88%; Fig. 3) at 24 h after surgery. Small study effect was not detected (Supplementary Fig. 3A) and the effect size remained stable when the Trim and Fill method was performed (Supplementary Fig. 3B). Although sensitivity analysis identified a change in the pooled effect size of pain scores when two studies [9,20] were excluded (Supplementary Fig. 4), this result should be interpreted with caution because of the small number of included studies.


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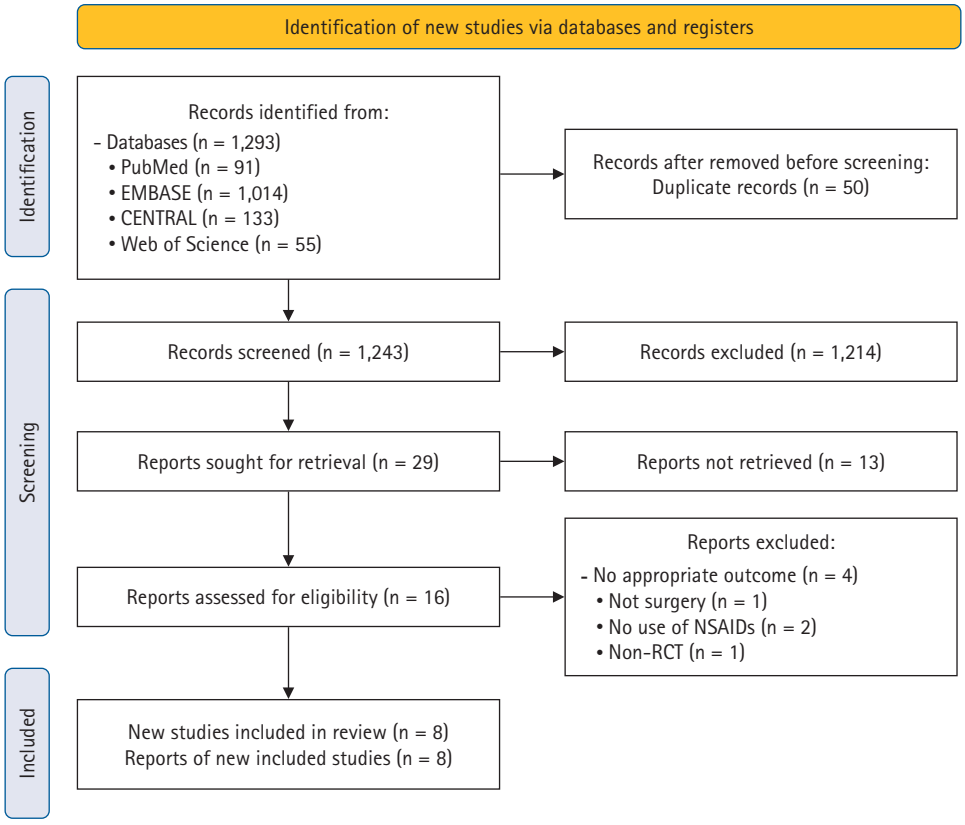


**Fig. 1.** Flow diagram of included studies in review and excluded studies. A total of 1,293 articles were found through electronic databases; however, 50 studies were duplicate findings. Among 1,243 studies, we regarded 1,214 articles as irrelevant after screening the title and abstract. Thirteen studies could not be retrieved. We reviewed the full texts of the remaining 16 articles and excluded eight irrelevant studies. Finally, a total of eight RCTs were included in the meta-analysis. NSAIDs: non-steroidal anti-inflammatory drugs, RCT: randomized controlled trial.

**Table 1.** Characteristics of Included Trials

| | Age (intervention/control) | Number of participants (intervention/control) | Surgery type | Anesthesia | Type of NSAIDs | Control drug | Timing of NSAIDs administration |
|---|---|---|---|---|---|---|---|
| Hala 2006 [18] | 73/73 | 40/46 | Open heart surgery | General | Parecoxib 40 mg | None | 30 min before surgery |
| Li 2013 [19] | 77/77 | 40/40 | Femoral head replacement surgery | CSE | Parecoxib 20 or 40 mg | Saline | Every 12 h after surgery |
| Mu 2017 [15] | 70/71 | 310/310 | Hip of knee replacement surgery | CSE | Parecoxib 40 mg | Saline | At the end of surgery and then every 12 h |
| Shen 2022 [21] | 69/68 | 60/60 | Video-assisted thoracoscopic pulmonary lobectomy | General | Flurbiprofen 100 mg | Intralipid | 20 min before incision |
| Wang 2019 [10] | 70/69 | 70/70 | Major non-cardiac surgery | General | Flurbiprofen 300 mg | Saline | Continuous infusion via PCA after surgery |
| Wang 2021 [20] | 79/80 | 35/35 | Femoral neck or intertrochanteric fracture surgery | NI | Parecoxib 40 mg | None | One day and 30 min before surgery |
| Wang 2023 [9] | 75/73 | 40/40 | Hip arthroplasty | General | Parecoxib 40 mg | Saline | 30 min before anesthesia and at the end of the surgery. |
| Zeiner 2023 [16] | 32/31 | 21/21 | Cruciate ligament surgery | General | Diclofenac 75 mg | Saline | Before emergence from anesthesia |

NSAIDs: non-steroidal anti-inflammatory drugs, CSE: combined spinal-epidural, NI: no information, PCA: patient-controlled analgesia.

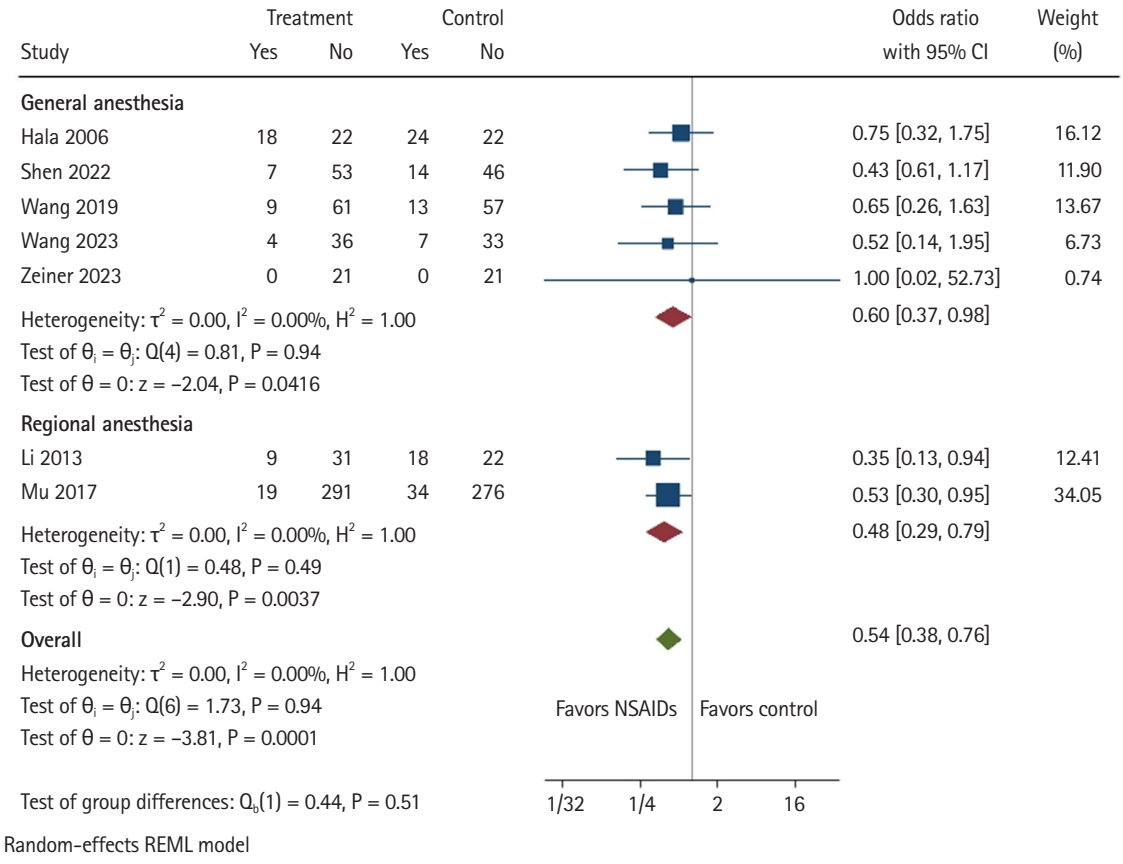


**Fig. 2.** Forest plot for the incidence of postoperative delirium between the NSAIDs and control groups. Significant differences were observed between the two groups. NSAIDs: non-steroidal anti-inflammatory drugs.

## Administration of opioids

Three studies [10,15,16] with a total of 802 participants were analyzed. The perioperative use of NSAIDs resulted in a reduction in the amounts of opioids used (MD: −2.88, 95% CI [−3.54, −2.22], P = 0.0000, $I^2$ = 0%; Fig. 4) during 24 h after surgery. It seems that there was publication bias as negative finding studies might be missing in the nonsignificant region based on the funnel plot (Supplementary Fig. 5A), and the Trim and Fill method imputed the estimated missing study in the funnel plot (Supplementary Fig. 5B). Sensitivity analyses revealed that pooled MD became insignificant by omitting studies conducted by Mu et al. [15] (MD: −2.55, 95% CI [−5.34, 0.23], P = 0.072; Supplementary Fig. 6). However, caution is warranted when interpretating these results owing to the limited number of studies included.

## Risk of bias

The overall risk of bias was assessed as 'low risk' in three studies [10,15,21], 'some concerns' in four studies [9,18–20], and 'high risk' in one study [16]. Two studies [18,20] were assessed as having 'some concerns' due to insufficient information regarding concealment and the pre-registered analysis plan. Li et al.'s study [19] lacked explicit details about the pre-registered analysis plan, leading to an assessment of 'some concerns' in that domain. Wang's study [9] lacked information about the pre-registered research plan, making it difficult to ascertain the study's intended objectives. Additionally, the absence of details regarding concealment made it challenging to determine whether there was bias in the outcome and intervention. In a study by Zeiner et al. [16], a considerable number of participants dropped out, resulting in a 'high risk' rating for missing outcome data. Additionally, the absence of information on the pre-registered plan led to 'some concerns' in the selection of the reported result domain, culminating in an overall 'high' risk of bias. The detailed assessment is shown in Supplementary Figs. 7A and 7B.

## Level of certainty of the evidence

The certainty levels for the incidence of postoperative delirium,


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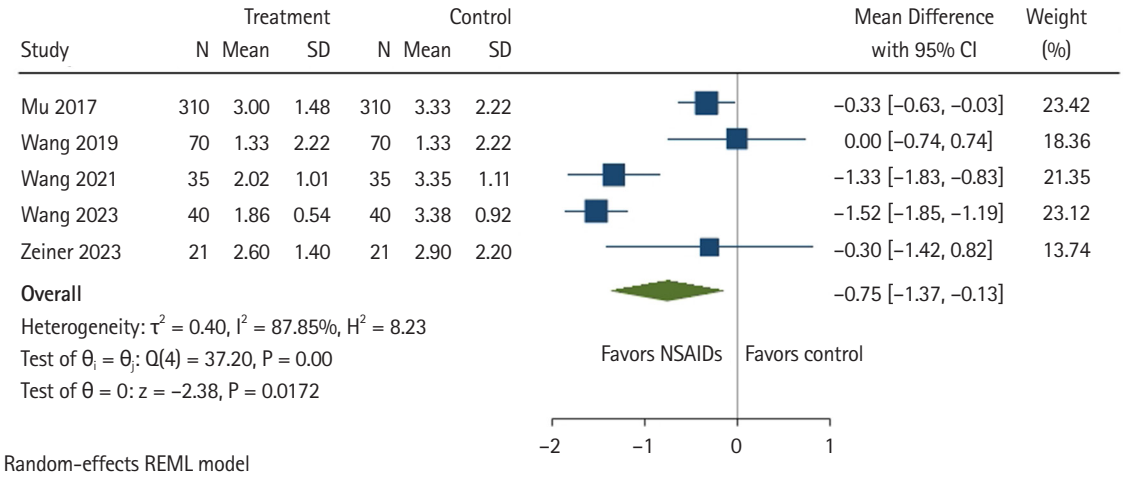


**Fig. 3.** Forest plot for postoperative pain score between the NSAIDs and control groups. The use of NSAIDs contributed to a reduction in postoperative pain (P = 0.0172). NSAIDs: non-steroidal anti-inflammatory drugs.

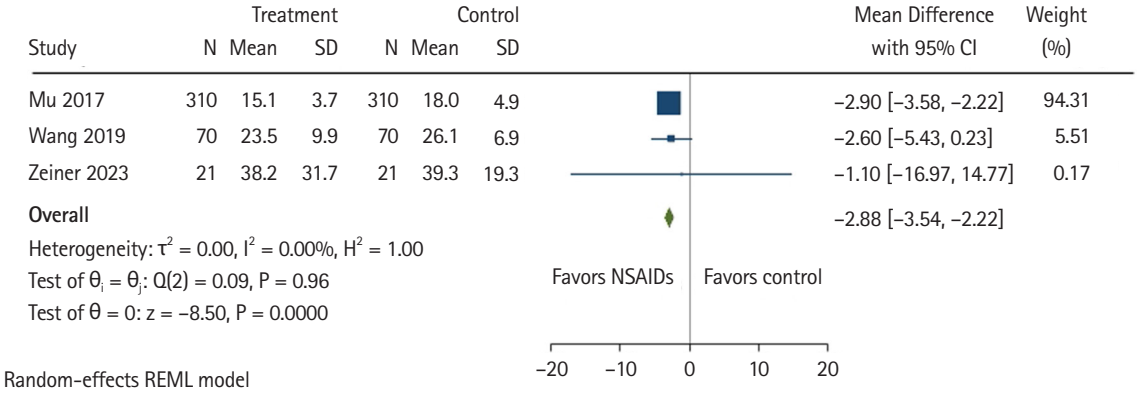


**Fig. 4.** Forest plot for postoperative opioid consumption between the NSAIDs and control groups. Postoperative opioid consumption was significantly lower in the NSAIDs group than in the control group (P = 0.0000). NSAIDs: non-steroidal anti-inflammatory drugs.

postoperative pain scores, and consumption of rescue analgesics were evaluated as moderate. Additional information on the certainty assessment is shown in Supplementary Table 2.

## Discussion

In the present meta-analysis, the perioperative administration of NSAIDs reduced the incidence of postoperative delirium, severity of postoperative pain, and need for opioids.

The reduction of the occurrence of postoperative delirium by 46% has a clinical meaning that NASIDs could be a valuable component for delirium-sparing strategies with relative low cost. Especially, when regional anesthesia was applied, the incidence decreased by 52%. So far, numerous etiologies for the development of postoperative delirium have been proposed, including neuroinflammation, pain, and opioid use [23]. Based on these risk factors and our results, the role of NSAIDs in preventing postoperative delirium can be considered in three ways.

First, as described earlier, delirium arises from neuroinflammation, and studies have been conducted to explore the potential effectiveness of mitigating delirium through the reduction of inflammation [19,24]. In patients undergoing surgery, inevitably, the inflammatory response can be triggered by surgical stimuli [25]. A hypothesis suggests that peripheral inflammation may induce neuroinflammation, potentially giving rise to cognitive decline in cases of delirium [26]. The inflammatory response results in the breakdown of the glycocalyx matrix within vascular endothelial cells, consequently heightening the permeability of the

blood-brain barrier [27,28]. This increased permeability facilitates greater entry of pro-inflammatory cytokines into the central nervous system (CNS), ultimately contributing to the worsening of postoperative cognitive decline [29]. As indicated by their name, NSAIDs inhibit cyclooxygenase, thereby preventing the synthesis of prostaglandins and suppressing inflammatory responses [30]. Based on these considerations, a hypothesis was formulated that reducing the inflammatory response through the use of NSAIDs might decrease the incidence of postoperative delirium. However, it is essential to exercise caution in interpreting this mechanism of NSAIDs' effects on postoperative delirium, as not all studies in this meta-analysis assessed the levels of inflammatory marker.

Second, the analgesic component of NSAIDs could not be overlooked. Pain has been considered one of the key components in developing delirium [23]. In particular, studies have reported clinical evidence that pre- and postoperative pain are related to the preoperative cognitive impairment and postoperative delirium [31,32]. In the present meta-analysis, NSAIDs showed a pain-reducing effect compared with the control group. Although direct association between the pain intensity and the occurrence of postoperative delirium could not be evaluated via this study, it is possible to suggest that the pain reduction observed with the administration of NSAIDs contributed to a decrease in the incidence of postoperative delirium. Additional well-designed clinical studies are needed to confirm the association between pain and postoperative delirium.

Finally, the role of opioids should be discussed. Opioids are the most commonly used drugs to control moderate to severe pain following surgery, providing patient comfort during the critical recovery period. Despite their efficacy, the use of opioids is associated with a range of adverse effects [33]. Furthermore, research indicates that opioid administration can increase the risk of postoperative delirium through several mechanism [34]. Opioids can have profound effects on the CNS by altering the neurotransmitter levels that disrupt normal cognitive processes and can lead to confusion and delirium [35]. This CNS alteration interferes with the brain's ability to maintain a stable and coherent state of consciousness, especially in the immediate postoperative period when patients are already vulnerable to cognitive disturbances. Additionally, opioids disrupt normal sleep patterns, reducing both the quality and quantity of restorative sleep essential for cognitive functioning and recovery [36]. This exacerbates cognitive dysfunction and increases the likelihood of delirium that is particularly concerning in postoperative patients who need adequate rest to heal and recover. The opioids-sparing effect of NSAIDs that was shown in this study might contribute to lowering the incidence of postoperative delirium. Nevertheless, further large clinical studies are required to explore the optimal use of opioids and to develop guidelines that minimize the occurrence of postoperative delirium while ensuring effective pain control.

There are several limitations within this study that should be acknowledged. First, there is a scarcity of included studies, limiting the diversity of data sources and potentially impacting the generalizability of the findings. Second, the variation in surgical procedures among the included studies introduces a confounding factor, as the degree of inflammation may vary depending on the type and duration of the surgery [37]. Consequently, analyzing only patients who underwent a single type of surgery may yield different results. Third, there is heterogeneity in the tools used to diagnose delirium. While most included studies employed diagnostic tools such as the CAM and MMSE, one utilized an internal scoring system, potentially compromising the reliability and consistency of the delirium assessment. Fourth, the age distribution of participants in the included studies was inconsistent. Postoperative delirium is known to occur more frequently in older adults [38,39]. The disparity in age ranges, such as in Zeiner's study [16] where participants were in their early thirties, introduces a potential bias. Consequently, restricting the study population to older individuals may yield different outcomes.

In conclusion, the use of NSAIDs resulted in reduced incidence of postoperative delirium, alleviation of postoperative pain, and decreased opioid consumption. However, the limitations related to potential publication bias and the small number of studies necessitate cautious interpretation of the results. Future research must address these issues for a more comprehensive understanding of the relationship between the use of NSAIDs and postoperative delirium.

## Funding

None.

## Conflicts of Interest

Jung-Hee Ryu has been an editor for the Korean Journal of Anesthesiology since 2019. However, she was not involved in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.

## Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reason-


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able request.

## Author Contributions

Su Yeon Kim (Conceptualization; Data curation; Formal analysis; Methodology)
Hyo-Seok Na (Conceptualization; Data curation; Investigation; Methodology; Validation; Writing – review & editing)
Jung-Hee Ryu (Conceptualization; Supervision; Validation; Writing – review & editing)
Hyun-Jung Shin (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing)

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## Supplementary Materials

Supplementary Table 1. Search strategy for each database.
Supplementary Table 2. Level of certainty for each outcome.
Supplementary Fig. 1. Funnel plot for the incidence of postoperative delirium.
Supplementary Fig. 2. Forest plot for sensitivity analysis of the incidence of postoperative delirium.
Supplementary Fig. 3. Funnel plot for the pain scores.
Supplementary Fig. 4. Forest plot for sensitivity analysis of postoperative pain.
Supplementary Fig. 5. Funnel plot for the opioid consumption.
Supplementary Fig. 6. Forest plot for sensitivity analysis of opioids consumption.
Supplementary Fig. 7. (A) Risk of bias summary. (B) Overall risk of bias as a summary plot.

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