Systematic Review and Meta-Analysis

Effect of prophylactic corticosteroids on postoperative neurocognitive dysfunction in the adult population: An updated systematic review, meta-analysis, and trial sequential analysis of randomised controlled trials

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ABSTRACT

Background and Aims: Postoperative neurocognitive dysfunction (PNCD) commonly occurs after surgery and prolongs hospital stays. Both direct noxious stimuli to the central nervous system and systemic inflammation have been implicated. Due to their potent anti-inflammatory effects, corticosteroids have been utilised to attenuate the incidence and severity of PNCD. This systematic review and meta-analysis strived to evaluate the prophylactic role of perioperative corticosteroids for PNCD. **Methods:** A search was run in pre-defined databases for randomised controlled trials (RCTs) assessing the role of corticosteroids in preventing PNCD. The incidence of PNCD within 1 month was the primary outcome. Secondary outcomes included the use of antipsychotic medications for the treatment, postoperative infection, and hospital length of stay. The results are exhibited as odds ratio (OR) and the mean difference (MD) with 95% confidence interval (CI). **Results:** Fifteen RCTs comprising 15,398 patients were included. The incidence of PNCD was significantly lower in the corticosteroid group than in the control group, with a pooled OR of 0.75 (95% CI 0.58, 0.96; $P = 0.02$; $I^2 = 66\%$). Trial sequential analysis showed the clinical benefit of corticosteroids in preventing PNCD; however, the requisite information size is still inadequate. The sub-group analysis supported the prophylactic effect of corticosteroids on delirium prevention but not on delayed neurocognitive recovery. **Conclusions:** Our meta-analysis revealed statistically significant protective effects of corticosteroids on the incidence of PNCD. However, further studies are still needed to confirm the protective role of this commonly used and relatively safe strategy for preventing PNCD.

Keywords: Corticosteroids, delayed neurocognitive recovery, delirium, dexamethasone, meta-analysis, postoperative cognitive dysfunction, post-operative neurocognitive dysfunction, systematic review, trial sequential analysis

INTRODUCTION

Postoperative neurocognitive dysfunction (PNCD) is commonly observed in the postoperative period, with an incidence varying between 11 and 51%.[1-3] It is generally divided into postoperative delirium (POD) and delayed neurocognitive recovery (dNCR), formerly

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known as postoperative cognitive dysfunction.[4] POD is a neuropsychiatric syndrome that develops in the immediate postoperative period. It is characterised by attention disturbance, disorientation to place and time, sleep deterioration, and memory impairment. This typically represents a change from baseline and fluctuates in severity during the day.[1] dNCR refers to a new cognitive impairment that develops up to 30 days after full recovery of consciousness from anaesthesia.[1] It typically persists beyond the expected pharmacological and physiological effects of anaesthetic drugs.

Increased age, the presence of neurological impairment, intraoperative blood loss, the type of surgery, the presence of a urinary catheter, electrolyte imbalance, uncontrolled pain, the use of opioids, and postoperative intensive care unit (ICU) admission all play important roles in the development of PNCD.[3,5] Its presence prolongs hospital stays, impairs the activities of daily living, and enhances the risk of delayed neurocognitive recovery, resulting in a negative financial implication on healthcare.[6,7]

The pathophysiology of PNCD is complex and still poorly understood. The inflammatory responses caused by surgical trauma and blood-brain barrier disruption associated with inflammation can cause injury to the brain.[8-10] Due to their potent anti-inflammatory effects, corticosteroids have been utilised in the perioperative period to attenuate the incidence and severity of PNCD. Previous meta-analyses have evaluated the efficacy of steroids in the prevention of PNCD in specific patient populations or evaluated the role of a single steroid, which limits the validity of their conclusions.[11,12] Li *et al*.[11] have pooled the data only for the efficacy of dexamethasone, whereas another meta-analysis included only patients undergoing cardiac surgery.[12] In a recently published meta-analysis, Xie *et al*.[13] delineated no benefit of adding corticosteroids to postoperative delirium; however, the authors did not calculate the requisite sample size to draw definite conclusions. The sample size of the meta-analysis increases by including more randomised controlled trials (RCTs), leading to greater precision in estimating the effect size or association between variables, which may lead to more reliable conclusions. Hence, we performed this updated systematic review and meta-analysis of RCTs evaluating the efficacy of different corticosteroids in preventing PNCD.

METHODS

Eligibility criteria

After registering the review with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42022339394), we used Population, Intervention, Comparators, Outcomes, Timing, and Settings (PICOTS) criteria to perform our review.[14]

Population: Adults ≥18 years of age who underwent surgery under anaesthesia.

Intervention: Patients who received corticosteroids during the perioperative period.

Comparators: Comparator group included patients who did not receive any corticosteroids.

Outcomes: The incidence of PNCD within 1 month was the primary outcome, as defined by the trial authors in their respective trials. The secondary outcomes studied were the severity of delirium, use of antipsychotic medications to treat PNCD, postoperative infection, mortality (all-cause mortality), and hospital length of stay.

Timing: 30 days postoperative.

Setting: Perioperative setting.

The methodology and study inclusion are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[15]

Data sources and searches

Two reviewers (JKM and NPS) independently conducted a literature search in PubMed, EMBASE, SCOPUS, and the Cochrane Central Registers of Controlled Trials (CENTRAL). The search was initially performed from the inception of the database until July 2022 and again updated in October 2022 to look for additional trials. MeSH terms *"cognitive dysfunction" OR "delirium" AND "corticosteroid" OR "dexamethasone" OR "methylprednisolone" AND "postoperative period"* were used in various combinations. There was no language restriction on the inclusion of studies. We planned to convert non-English studies using an online translator (https://www.enago.com/translation/). Furthermore, we manually searched the bibliography of pertinent publications, and those fulfilling the inclusion criteria were

incorporated. Zotero version 5.0 (Corporation for Digital Scholarship) was utilised to catalogue the publications. The detailed search strategy is provided in the Supplementary File 1.

Study eligibility

We reviewed RCTs that compared any corticosteroid with a placebo or no steroid in the perioperative period with the occurrence of PNCD in patients getting anaesthesia for undergoing surgery. We excluded studies involving paediatric and animal populations and non-randomised trials. Trials were excluded if a comparison between two steroids or different doses of the same steroid was evaluated without any control treatment arm. Treatment arms were clustered as active if different doses of steroids were compared with a non-active comparator.

Study selection

Two investigators (NPS and JKM) assessed the abstract individually and screened eligible full text. Any discrepancy was resolved by discussion and, if required, by harmonisation by a third author (PMS).

Data abstraction and outcome measures

Trial data were extracted by two of the authors (NPS and JKM). The lead author (NPS) reviewed all variable values and extracted all values required for the analysis. The data extracted included trial design, publication year and country, number of patients, type of surgery performed, corticosteroid, and measured dose and outcomes. Data on the type of the control treatment, mode of intraoperative anaesthesia, incidence of delirium, scoring systems used to measure delirium, the severity of delirium, need for antipsychotic medication, postoperative infection, length of hospital stay, and mortality were collected. The extracted data were recorded using Microsoft Excel (Microsoft Corp., Redmond, WA, USA). If the outcome data were not reported, the trial principal investigators were contacted via email for additional information. Data are presented as the median and interquartile range (IQR) and were transformed to the mean and standard deviation (SD) utilising Hozo's formula ($x \approx a + 2m + b/4$, median (m), the low and high end of the range (a and b, respectively)).[16]

Risk of bias assessment of individual trials and certainty of evidence across trials

The assessment of risk of bias (ROB) utilised the updated Cochrane risk-of-bias tool for randomised trials (ROB2) criteria.[17] The tool employs questions to answer five domains: randomisation process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. The overall ROB was expressed as low risk, some concerns, or high risk. The overall certainty of evidence across various outcomes was judged using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) guidelines.[18] Based on the extent of bias observed across these criteria, the pooled outcomes were categorised from high quality to very low quality.

Data analysis

The statistical analysis was performed using a Comprehensive Meta-Analysis (Version 3.3, Biostat Inc. 2014, Englewood, NJ, USA). This software evaluated the weighted mean differences (MDs) for continuous data and the Mantel–Haenszel (MH) odds ratio (OR) for categorical data between the corticosteroid and control groups, with an overall pooled estimate. The I^2 statistic, indicating trial heterogeneity, was completed for each outcome. We considered the heterogeneity low if I^2 was $<50\%$,[19] and we chose a fixed-effects model; otherwise, a random-effects model was selected. Forest plots were generated to estimate the treatment effects. Qualitative reporting was done for the outcomes if data could be retrieved from less than three trials or 100 patients. All reported *P* values were two-sided; $P < 0.05$ was considered to indicate statistical significance. Publication bias was judged by visually inspecting funnel plots of the standard error of the mean (SEM) difference (y-axis) as a function of the MD (x-axis). The results were further quantified with Egger's linear regression test.

We performed the sub-group analysis according to the type of PNCD (POD or dNCR), surgery (cardiac or non-cardiac), and the incidence of PNCD. Due to the limited pooled data, we could not perform sub-group analyses depending on the dose and type of corticosteroid.

Trial sequential analysis (TSA) was performed for the primary outcome with TSA Viewer (Version 0.9.5.10 Beta, Copenhagen Trial Unit, 2016, Copenhagen, Denmark) to ascertain whether the accumulated sample size was appropriately powered and avoid random error. Conventional (with an alpha of 5%) and alpha O'Brien boundaries (for random-effects modelling with an alpha of 5% and a beta of 20%) were created. The heterogeneity correction in the TSA was set to variance-based, and the random-effects model was

used. For the TSA modelling, the requisite "information size" (IS) was considered using two approaches (the classical boundary and the O'Brien–Fleming alpha spending boundary). The cumulative, sequential Z score curve was constructed by calculating Z statistics from each study. Once the cumulative Z curve crosses the TSA monitoring boundary, a firm conclusion can be drawn that there is a significant difference before achieving the IS.

RESULTS

Literature search

Figure 1 shows the PRISMA diagram depicting the trial inclusion/elimination process. A total of 9138 records were identified through databases, and an additional six publications were identified through the reference lists of relevant publications. After de-duplication and screening of titles and abstracts, 22 full texts were assessed for eligibility for final inclusion. Fifteen RCTs enrolling 15,398 patients were finally included.[20-34] Of these, 7832 patients were enroled in the corticosteroid group, and 7566 were assigned to the control group. No conference abstracts published in peer-reviewed journals or non-English RCTs met our inclusion criteria.

Overview of included trials

The characteristics of the included trials are shown in Table 1. The sample size of each arm in the included trials ranged from 30 to 3755 patients. Patients in two trials received either general or neuraxial

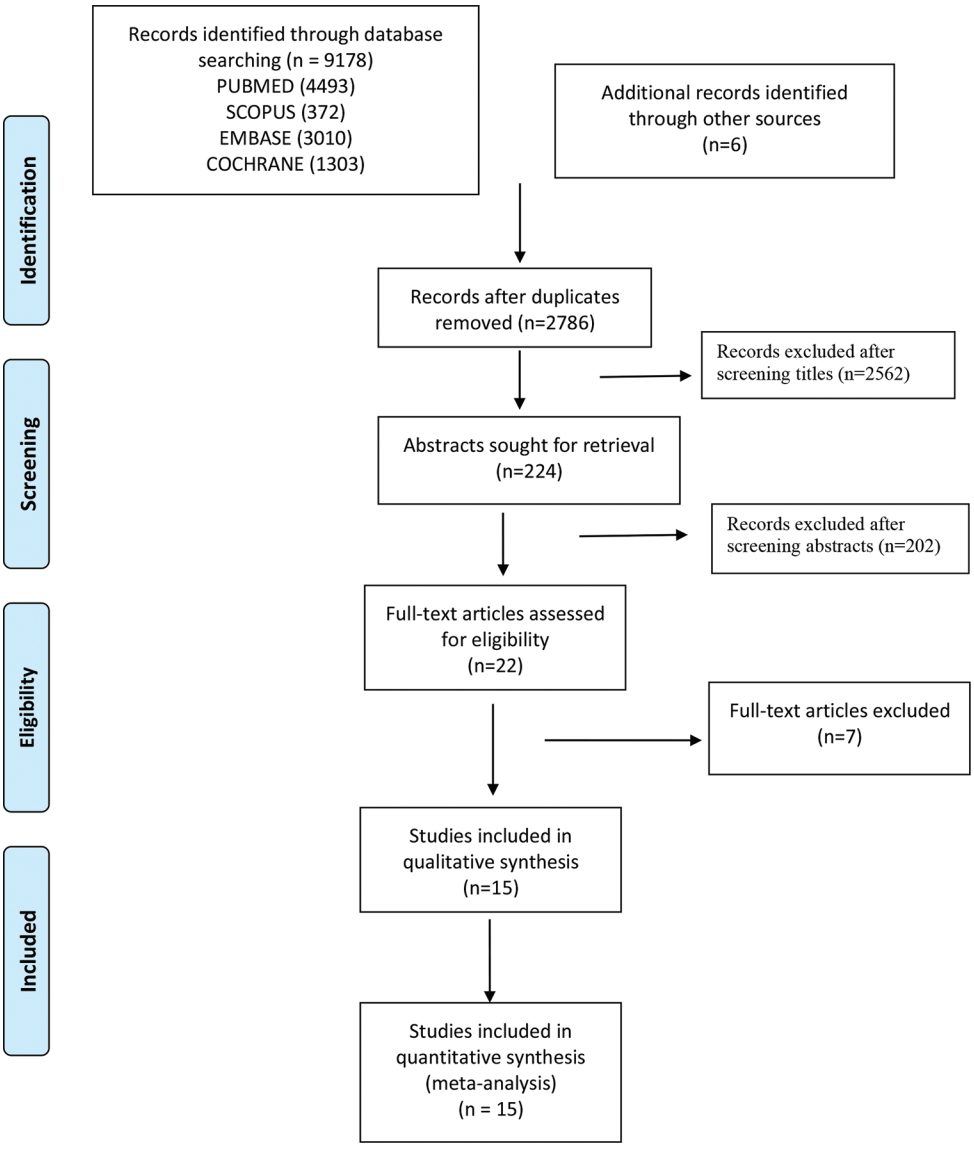

Figure 1: Flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines showing the literature search results

Table 1: Characteristics of the included trials

Author Country	Type of surgery	Age criteria (years)	Mode of intraoperative anaesthesia	Groups	Postoperative neurocognitive dysfunction assessment method
Clemmesen 2018[20] Denmark	Hip fracture surgery	≥65	Epidural anaesthesia/ Intravenous general anaesthesia	Methyl prednisone 125 mg (59) Placebo (58)	CAM
Dieleman 2018[21] Netherlands	Cardiac surgery	≥18	Intravenous/inhalational general anaesthesia	Dexamethasone 1 mg/kg (2235) Placebo (2247)	Antipsychotic drug usage
Fang 2014[22] China	Microvascular decompression	40-60	Intravenous general anaesthesia with BIS maintenance between 40-60	Dexamethasone 1 mg/kg (320) Dexamethasone 2 mg/kg (315) Placebo (319)	Multiple scales
Gądek 2021[23] Poland	Total hip arthroplasty	>65	Spinal anaesthesia	Methyl prednisone 125 mg (39) Placebo (38)	NM
Glumac 2017[24] Croatia	Cardiac surgery	41-84	Inhalational general anaesthesia with BIS maintenance between 40-55	Dexamethasone 1 mg/kg (80) Placebo (81)	Multiple scales
Hauer 2012[25] Germany	Cardiac surgery	NM	General anaesthesia	Hydrocortisone 100 mg followed by tapering infusion for 4 days (56) Placebo (55)	DSM-IV
Kluger 2021[26] New Zealand	Hip fracture surgery	≥65	Spinal anaesthesia/ intravenous general anaesthesia with BIS maintenance between 40-60	Dexamethasone 20 mg (40) Placebo (39)	4AT, MDAS
Mardani 2013[27] Iran	Cardiac surgery	≤80	General anaesthesia	Dexamethasone 8 mg 8 hourly*3 days (43) Placebo (50)	MMSE and psychiatric interview
Ottens 2014[28] Netherlands	Cardiac surgery	≥18	Inhalational general anaesthesia	Dexamethasone 1 mg/kg (140) Placebo (138)	Multiple scales
Qiao 2015[29] China	Oesophageal carcinoma surgery	65-75	Intravenous/inhalational general anaesthesia with BIS maintenance between 50-60	Methyl prednisone 10 mg/kg (30) Control (60)	MMSE and MoCA
Royse 2017[30] Australia, Canada, and the USA	Cardiac surgery	≥18	General anaesthesia	Methyl prednisone 250 mg*2 (250) Placebo (248)	CAM-ICU
Sauër 2014[31] Netherlands	Cardiac surgery	≥18	General anaesthesia	Dexamethasone 1 mg/kg (318) Placebo (325)	CAM-ICU
Valentin 2016[32] Brazil	Non-cardiac, non-neurosurgery	≥60	Intravenous general anaesthesia with BIS maintenance between 35-45 and 46-55	Dexamethasone 8 mg (68) Control (72)	Multiple scales
Whitlock 2015[33] Multi-country	Cardiac surgery	≥18	General anaesthesia	Methyl prednisone 250 + 250 mg (3755) Placebo (3752)	CAM
Xiang 2022 China[34]	Laparoscopic gastrointestinal surgery	65-80	Intravenous general anaesthesia with BIS maintenance between 40-60	Methyl prednisone 2 mg/kg (84) Placebo (84)	CAM

BIS, bispectral index; CABG, coronary artery bypass graft; CAM, confusion assessment method; CAM-ICU, confusion assessment method for intensive care units; DSM-IV, Diagnostic and Statistical Manual of the American Psychiatric Association IVth Edition; MDAS=Memorial Delirium Assessment Scale; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; NM=Not mentioned

anaesthesia[20,26]; one trial participant received spinal anaesthesia[23], and the rest received general anaesthesia. Two trials involved three arms,[22,29] one trial involved four arms,[32] and the remaining studies involved two arms. The patient's depth of anaesthesia was maintained in six trials according to the processed electroencephalogram (EEG).[22,24,26,29,32,34] Corticosteroids were administered before induction in all trials, except for one[21], where the administration occurred post-induction. Dexamethasone was

the most frequently studied steroid in eight trials[21,22,24,26-28,31,32], followed by methylprednisone in six trials[20,23,29,30,33,34] and hydrocortisone in one trial.[25] Eleven trials administered a single dose of corticosteroids;[20,21,23,24,26,28,29,31,32,34] the remaining trials administered multiple doses to the trial participants. Various delirium-specific instruments have been used for diagnosing delirium and/or assessing delirium severity, with most studies using more than one instrument. The Confusion Assessment Method (CAM) was the most frequently used instrument to diagnose POD, and the dNCR was assessed by multiple scales in most of the included trials. Individual studies used the delirium severity measurement tool to define mild, moderate, and severe delirium. Four studies reported the use of antipsychotic medication for the treatment of delirium in the postoperative period.[20,26,31,34] Two studies observed PNCD for 30 days,[20,27] whereas the remaining studies observed it for a shorter period, within a week.

Risk of bias assessment and publication bias

The ROB assessment for each trial is depicted in Figure 2a. Regarding the risk for overall bias, two of the 15 RCTs were deemed high risk; one had some concerns, and the rest were considered low risk. The graphical funnel plot constructed for the primary outcome appeared to be symmetrical, and this finding was further confirmed using Egger's test, which showed no statistical significance [Figure 2b]. The intercept was -1.11 ($P = 0.127$). Hence, any significant publication bias is unlikely due to corticosteroids' effects on PNCD.

Incidence of PNCD

Fourteen RCTs (total 15,308 patients: 7802 patients: control group; 7506 patients: corticosteroid group) provided data on the outcome for statistical pooling [Figure 3a]. The incidence of PNCD was significantly lower in the corticosteroid group than in the control group, with a pooled OR of 0.75 (95% CI 0.58, 0.96; $P = 0.02$; $I^2 = 66\%$). The GRADE certainty of the evidence for the effect was moderate. The results of the sequential removal of individual studies demonstrated no clear outlier.

Trial sequential analysis

To construct the alpha-spending boundary, an alpha error of less than 5% and a power of 80% were used [Figure 3b]. As our sample size (15,308) was less than the requisite sample size of 18,445, there is a likelihood of a false-positive beneficial effect of corticosteroids on PNCD. This finding suggests that future results of the beneficial effects of corticosteroids may change with additional trials. However, the cumulative Z score crossed the trial sequential monitoring boundary for the benefit of corticosteroids on the incidence of PNCD compared to the control.

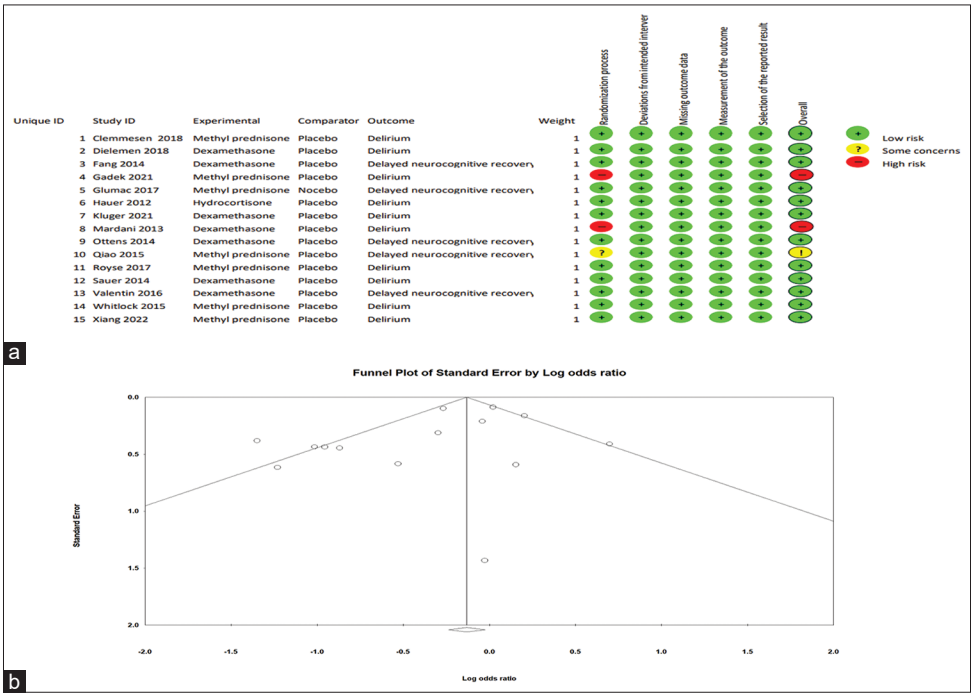

Figure 2: (a) Risk of bias summary of the included studies according to the Cochrane Collaboration guidelines. *Green, red, and yellow circles indicate low, high, and unclear risk of bias, respectively.* (b) Funnel plot for publication bias for postoperative neurocognitive dysfunction

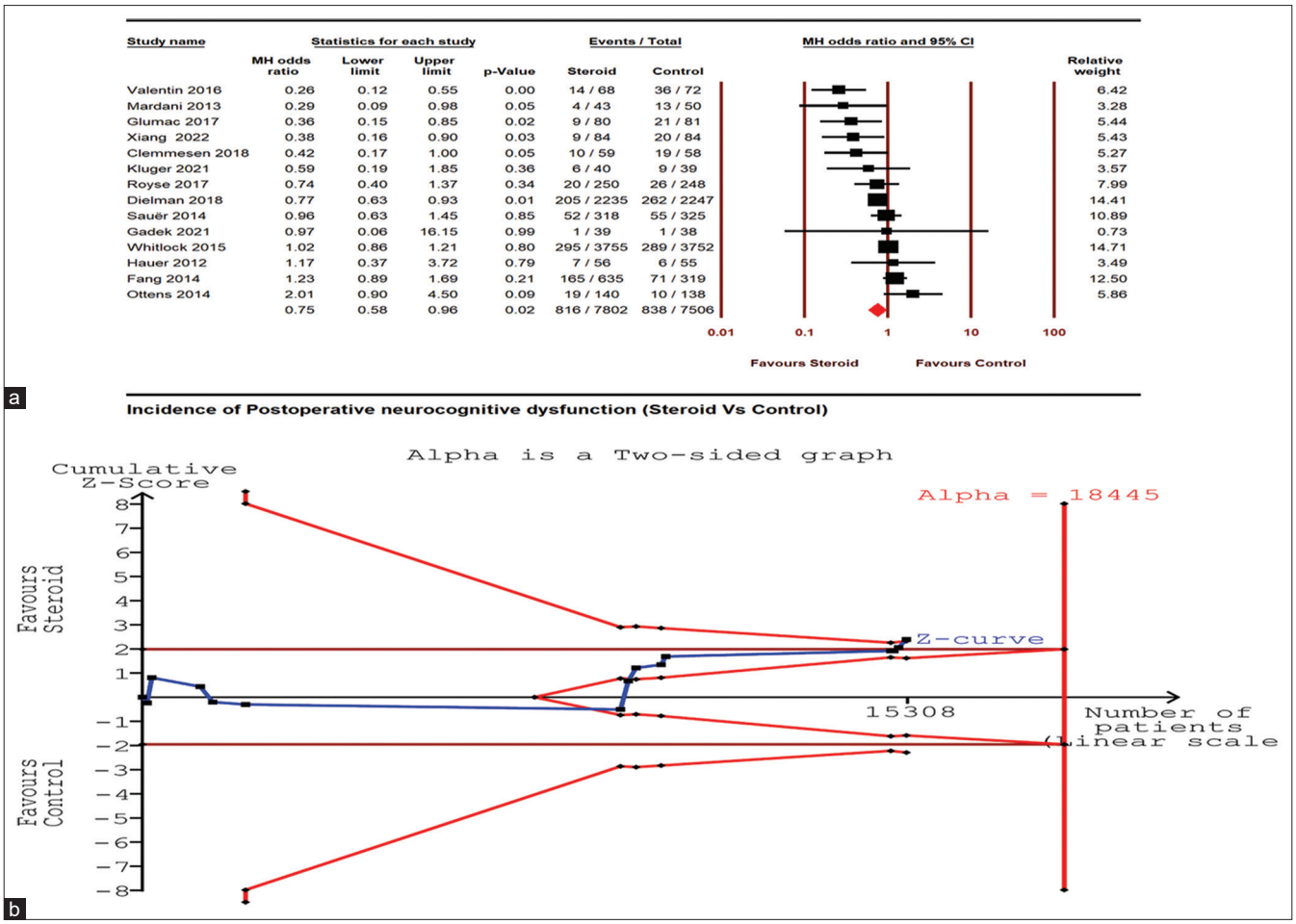

Figure 3: (a) Forest plot showing the effect of corticosteroids on postoperative neurocognitive dysfunction. (b) Trial sequential analysis (TSA) for intraoperative analgesic supplementation. *The lower half of the graph below the zero axis represents the area of advantage with respect to the control group, and the upper half represents the advantage area with respect to the steroid group. The solid black squares indicate the cumulative z score with the addition of each of the seven trials in chronological order. The brown lines on the Y-axis represent the conventional model boundaries for TSA with an alpha error of 5%. The red lines represent the alpha-spending boundary (upper O'Brien Fleming, with an alpha of 5% and a low risk of bias). The minimum required IS for the alpha-spending boundary model is 18,445 (vertical line intersecting the X-axis in red)*

Sub-group analyses

Sub-group analyses were performed on the type of PNCD (POD and dNCR) and type of surgery. Figure 4a shows that there was a statistically significant decrease in the incidence of POD with the use of steroids (OR 0.78; 95% CI 0.63, 0.97; $P = 0.03$), whereas the incidence of dNCR did not significantly decrease in the corticosteroid group (OR 0.71; 95% CI 0.29, 1.72; $P = 0.45$). Figure 4b shows that the sub-group analysis based on surgery did not reveal significant benefits of corticosteroids in either cardiac (OR 0.85; 95% CI 0.67, 1.10; $P = 0.22$) or non-cardiac surgery patients (OR 0.81; 95% CI 0.64, 1.02; $P = 0.08$).

Postoperative antipsychotic medication requirement

The data for the outcomes were pooled from four trials comprising 1007 participants. There was an insignificant difference in the odds of the need for antipsychotic medication between the two groups [OR 1 (95% CI 0.61, 1.64; $P = 1$; $I^2 = 0\%$)].

Severity of PNCD

A trial by Kluger *et al*.[26] reported delirium severity as the highest value of the Memorial Delirium Assessment Scale (MDAS), and the scores were significantly lower in the dexamethasone group.

Hospital length of stay

Six studies with 5098 patients (corticosteroid group: 2540 patients and control group: 2558 patients) reported a significant difference in the LOS with the use of corticosteroids, with an MD of -0.80 (95% CI -1.09, -0.52; $P < 0.001$; $I^2 = 36\%$).

Post-operative infection

Pooled data from five studies with 12,319 patients showed that patients in the corticosteroid group were

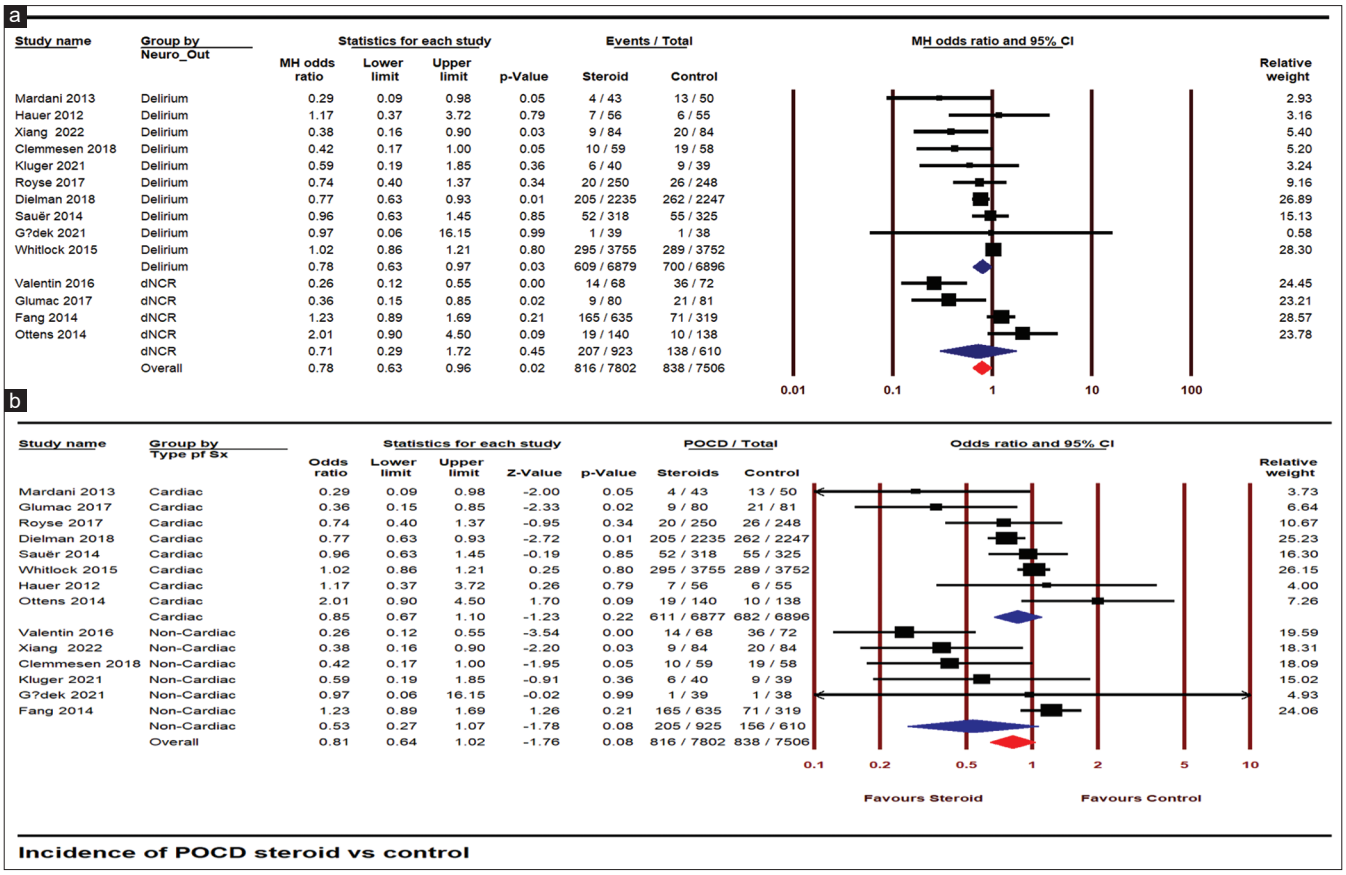

Figure 4: (a) Subgroup analysis for the incidence of postoperative delirium and delayed neurocognitive recovery with corticosteroids. (b) Subgroup analysis of the effect of the type of surgery on the incidence of postoperative neurocognitive dysfunction. dNCR=Delayed neurocognitive recovery, POCD=Postoperative cognitive dysfunction, CI=Confidence interval

not at increased risk of postoperative infection [OR -0.89 (95% CI 0.59, 1.34; $P = 0.58$; $I^2 = 79\%$)].

All-cause 30-day mortality

There was no significant difference between the groups regarding 30-day mortality, with an OR of 0.87 (95% CI, 0.71, 1.06; $P = 0.16$; $I^2 = 0\%$).

DISCUSSION

We performed a systematic review meta-analysis and TSA of RCTs evaluating the role of perioperative corticosteroids in preventing PNCD in adult surgical patients. Moderate certainty evidence suggests that corticosteroids had a statistically significant protective effect on PNCD compared to those in the control group. The TSA revealed that more RCTs are required to provide a more decisive answer regarding the effect of steroids on the prevention of PNCD. The sub-group analysis supported the prophylactic effect of corticosteroids on delirium prevention but not on the dNCR. When the length of hospital stay decreased with corticosteroid treatment, the risks of post-operative infection and all-cause 30-day mortality did not differ between patients who did or did not receive corticosteroids.

Neurological complications, including PNCD after surgery, have been attributed to neuroinflammation. Corticosteroids given before or during surgery counter the detrimental effect of inflammation induced by surgery and anaesthesia. In our analysis, we observed that the administration of steroids reduced the incidence of PNCD. A recent meta-analysis conducted to determine the prophylactic efficacy of steroids in PNCD patients concluded that there was no significant difference compared with that of the control group.[13] The lack of benefit on PNCD with corticosteroids seen in this meta-analysis could be attributed to the relatively small number of included patients compared to our sample size. The TSA of our meta-analysis also revealed that more RCTs are still required to reach any definite conclusions.

Steroids are among the most extensively used drugs in the perioperative period, mainly for postoperative

nausea and vomiting, as an adjunct to analgesia, acute hyperreactive airways, anaphylaxis, and post-extubation stridor.[35] As the drug is safe in a single dose and has multiple benefits in the perioperative period, its effectiveness should be thoroughly explored before ruling out its role in the prevention of PNCD.

PNCD remains an area of concern and impacts perioperative morbidity and mortality, especially in high-risk patient populations. PNCD has a multi-factorial aetiology, and impacting only one pathway may not be enough to prevent its development. Patient age, pre-operative cognitive function, major cardiac or non-cardiac surgery, surgery duration, and haemodilution are a few precipitating factors for the development of PNCD, and a single intervention by itself may not be effective. It has been proposed that implementing and advancing delirium prevention protocols specifically targeting high-risk surgical populations may significantly improve peri-operative patient care.[36] Hence, studies evaluating a bundled approach targeting multiple pathways of neurological injury during the perioperative period may be needed to help prevent the development of this postoperative complication. Corticosteroids could be one of the various components of this bundled approach.

Limitations

There are several limitations to this meta-analysis. Cautious interpretation of the conclusion is advised due to the limited evidence and the heterogeneity in the outcomes, mainly clinical heterogeneity, such as the time and dose of dexamethasone administered, the type of surgery, different periods for the assessment of PNCD, and the different definitions and evaluation tools of PNCD, which may limit the accuracy and dependability of the results. Moreover, the lack of standardised screening criteria for the estimation of the pre-operative existence of neurocognitive functions was not addressed in the included population. Most of the included trials did not include patients at high risk of developing PNCD; therefore, the significance of these results may be limited.

CONCLUSIONS

Our meta-analysis revealed statistically significant protective effects of the use of corticosteroids on the incidence of postoperative neurocognitive dysfunction, and TSA revealed that an adequate effect size was still not achieved. Hence, we believe that further studies should be conducted to confirm the role of this commonly used and relatively safe drug in preventing postoperative neurocognitive dysfunction. Future RCTs should focus on bundled approaches targeting multiple pathways of neurological injury during the peri-operative period and targeting high-risk patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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REFERENCES

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014;383:911-22.
2. Mahanna-Gabrielli E, Schenning KJ, Eriksson LI, Browndyke JN, Wright CB, Culley DJ, *et al*. State of the clinical science of perioperative brain health: Report from the American Society of Anesthesiologists brain health initiative summit 2018. Br J Anaesth 2019;123:464-78.
3. American Geriatrics Society expert panel on postoperative delirium in older adults. Postoperative delirium in older adults: Best practice statement from the American Geriatrics Society. J Am Coll Surg 2015;220:136-48.e1.
4. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, *et al*. Recommendations for the nomenclature of cognitive change associated with anesthesia and surgery-2018. Anesth Analg 2018;127:1189-95.
5. Bramley P, McArthur K, Blayney A, McCullagh I. Risk factors for postoperative delirium: An umbrella review of systematic reviews. Int J Surg 2021;93:106063. doi: 10.1016/j.ijsu.2021.106063.
6. Gleason LJ, Schmitt EM, Kosar CM, Tabloski P, Saczynski JS, Robinson T, *et al*. Effect of delirium and other major complications on outcomes after elective surgery in older adults. JAMA Surg 2015;150:1134-40.
7. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med 2008;168:27-32.
8. Swarbrick CJ, Partridge JSL. Evidence-based strategies to reduce the incidence of postoperative delirium: A narrative review. Anaesthesia 2022;77(Suppl 1):92-101.
9. Patel M, Onwochei DN, Desai N. Influence of perioperative dexmedetomidine on the incidence of postoperative delirium in adult patients undergoing cardiac surgery. Br J Anaesth 2022;129:67-83.
10. Lopez MG, Hughes CG, DeMatteo A, O'Neal JB, McNeil JB,

Shotwell MS, *et al*. Intraoperative oxidative damage and delirium after cardiac surgery. Anesthesiology 2020;132:551-61.
11. Li LQ, Wang C, Fang MD, Xu HY, Lu HL, Zhang HZ. Effects of dexamethasone on postoperative cognitive dysfunction and delirium in adults following general anaesthesia: A meta-analysis of randomised controlled trials. BMC Anesthesiol 2019;19:113. doi: 10.1186/s12871-019-0783-x.
12. Liu W, Wang Y, Wang J, Shi J, Pan J, Wang D. Effects of glucocorticoids on postoperative delirium in adult patients undergoing cardiac surgery: A systematic review and meta-analysis. Clin Ther. 2021;43:1608-21.
13. Xie X, Gao R, Chen H. Effects of glucocorticoids on postoperative neurocognitive disorders in adult patients: A systematic review and meta-analysis. Front Aging Neurosci 2022;14:939848. doi: 10.3389/fnagi. 2022.939848.
14. Riva JJ, Malik KM, Burnie SJ, Endicott AR, Busse JW. What is your research question? An introduction to the PICOT format for clinicians. J Can Chiropr Assoc 2012;56:167-71.
15. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160. doi: 10.1136/bmj. n160.
16. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13. doi: 10.1186/1471-2288-5-13.
17. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. RoB 2: A revised tool for assessing risk of bias in randomized trials. BMJ 2019;366:l4898. doi: 10.1136/bmj. l4898.
18. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from: https://www.grad epro. org. [Last assessed on 2023 Dec].
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
20. Clemmesen CG, Lunn TH, Kristensen MT, Palm H, Foss NB. Effect of a single pre-operative 125 mg dose of methylprednisolone on postoperative delirium in hip fracture patients; A randomised, double-blind, placebo-controlled trial. Anaesthesia 2018;73:1353-60.
21. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, *et al*. Intraoperative high-dose dexamethasone for cardiac surgery: A randomized controlled trial. JAMA 2012;308:1761-7.
22. Fang Q, Qian X, An J, Wen H, Cope DK, Williams JP. Higher dose dexamethasone increases early postoperative cognitive dysfunction. J Neurosurg Anesthesiol 2014;26:220-5.
23. Gądek A, Liszka H, Zając M. The effect of pre-operative high doses of methylprednisolone on pain management and convalescence after total hip replacement in elderly: A double-blind randomized study. Int Orthop 202;45:857-63.
24. Glumac S, Kardum G, Sodic L, Supe-Domic D, Karanovic N. Effects of dexamethasone on early cognitive decline after cardiac surgery: A randomised controlled trial. Eur J Anaesthesiol 2017;34:776-84.
25. Hauer D, Weis F, Campolongo P, Schopp M, Beiras-Fernandez A, Strewe C, *et al*. Glucocorticoid-endocannabinoid interaction in cardiac surgical patients: Relationship to early cognitive dysfunction and late depression. Rev Neurosci 2012;23:681-90.
26. Kluger MT, Skarin M, Collier J, Rice DA, McNair PJ, Seow MY, *et al*. Steroids to reduce the impact on delirium (STRIDE): A double-blind, randomised, placebo-controlled feasibility trial of pre-operative dexamethasone in people with hip fracture. Anaesthesia 2021;76:1031-41.
27. Mardani D, Bigdelian H. Prophylaxis of dexamethasone protects patients from further post-operative delirium after cardiac surgery: A randomized trial. J Res Med Sci 2013;18:137-43.
28. Ottens TH, Dieleman JM, Sauër AM, Peelen LM, Nierich AP, de Groot WJ, *et al*. Effects of dexamethasone on cognitive decline after cardiac surgery: A randomized clinical trial. Anesthesiology 2014;121:492-500.
29. Qiao Y, Feng H, Zhao T, Yan H, Zhang H, Zhao X. Postoperative cognitive dysfunction after inhalational in elderly patients undergoing major surgery: The influence of anesthetic technique, cerebral injury and systemic inflammation. BMC Anesthesiol 2015;15:154. doi: 10.1186/s12871-015-0130-9.
30. Royse CF, Saager L, Whitlock R, Ou-Young J, Royse A, Vincent J, *et al*. Impact of methylprednisolone on postoperative quality of recovery and delirium in the steroids in cardiac surgery trial: A randomized, double-blind, placebo-controlled substudy. Anesthesiology 2017;126:223-33.
31. Sauër AM, Slooter AJ, Veldhuijzen DS, van Eijk MM, Devlin JW, van Dijk D. Intraoperative dexamethasone and delirium after cardiac surgery: A randomized clinical trial. Anesth Analg 2014;119:1046-52.
32. Valentin LS, Pereira VF, Pietrobon RS, Schmidt AP, Oses JP, Portela LV, *et al*. Effects of single low dose of dexamethasone before noncardiac and nonneurologic surgery and general anesthesia on postoperative cognitive dysfunction-A phase III double blind, randomized clinical trial. PLoS One 2016;11:e0152308. doi: 10.1371/journal.pone. 0152308.
33. Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, *et al*. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): A randomised, double-blind, placebo-controlled trial. Lancet 2015;386:1243-53.
34. Xiang XB, Chen H, Wu YL, Wang K, Yue X, Cheng XQ. The effect of preoperative methylprednisolone on postoperative delirium in older patients undergoing gastrointestinal surgery: A randomized, double-blind, placebo-controlled trial. J Gerontol A Biol Sci Med Sci 2022;77:517-23.
35. Myles PS, Corcoran T. Benefits and risks of dexamethasone in noncardiac surgery. Anesthesiology 2021;135:895-903.
36. Hughes CG, Boncyk CS, Culley DJ, Fleisher LA, Leung JM, McDonagh DL, *et al*. American society for enhanced recovery and perioperative quality initiative joint consensus statement on postoperative delirium prevention. Anesth Analg 2020;130:1572-90.