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Clinical Study

Dexmedetomidine as an anesthetic adjuvant for intracranial procedures: Meta-analysis of randomized controlled trials

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ABSTRACT

This meta-analysis aimed to systematically collect the current evidence regarding the efficacy and safety of dexmedetomidine (DEX) as an anesthetic adjuvant for patients undergoing intracranial surgery. A systematic literature search of randomized controlled trials (RCT) was conducted to compare DEX with placebo or opioids in patients undergoing intracranial procedures. Hemodynamic data, opioid consumption, and recovery parameters were pooled. Eight RCT were included. Results showed that patients treated with DEX required less intraoperative treatment for hypertension and hypotension (risk ratio [RR] = 0.48, 95% confidence interval [CI] 0.31–0.75, $p = 0.001$; and RR = 0.66, 95% CI 0.43–1.01, $p = 0.05$, respectively) and less postoperative treatment for hypertension and tachycardia (RR = 0.37, 95% CI 0.17–0.79, $p = 0.01$; and RR = 0.14, 95% CI 0.03–0.59, $p = 0.007$, respectively) compared with placebo. Patients also had lower mean arterial pressure and heart rate when extubated (mean difference [MD] = −9.74 mmHg, 95% CI −12.35 to −7.12, $p < 0.00001$; and MD = −16.35 beats/minute, 95% CI −20.00 to −12.70, $p < 0.00001$, respectively), a lower intraoperative additional fentanyl consumption (MD = −0.78 μg/kg, 95% CI −1.51 to −0.05, $p = 0.04$), and lower postoperative antiemetic requests (RR = 0.51, 95% CI 0.33–0.80, $p = 0.003$). DEX may not increase extubation time, postoperative P_aCO_2, or the risk of perioperative bradycardia. Only a small number of RCT are available, but meta-analysis shows evidence that DEX as an anesthetic adjuvant during intracranial procedures leads to better perioperative hemodynamic control, less intraoperative opioid consumption, and fewer postoperative antiemetic requests.

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1. Introduction

Perioperative hemodynamic stability is of utmost importance in neurosurgical patients. Hypertension during surgery can cause bleeding or edema in the operative field, and an abrupt elevation of arterial blood pressure (BP) during the recovery period is also associated with postoperative hematoma and a prolonged hospital stay [1]. Hypotension, on the other hand, increases the risk of cerebral ischemia because autoregulation of cerebral blood flow is often impaired near tumors or surgically traumatized areas [2]. Moreover, cerebrovascular responses may increase intracranial pressure and reduce cerebral perfusion pressure, which can exacerbate ischemia damage. In addition, rapid recovery from anesthesia to facilitate immediate evaluation of neurological status is preferred in neurosurgical patients. Thus, anesthetic techniques that improve perioperative hemodynamics and allow early neurological evaluation without increasing the incidence of possible adverse events (such as nausea and vomiting, increased intracranial pressure, respiratory depression, or prolonged sedation) are desirable.

Dexmedetomidine (DEX), a highly selective α-2 adrenoceptor agonist that provides sedation, analgesia, and anxiolytic effects, might be useful in neurosurgical procedures [3,4]. There are several randomized controlled trials (RCT) focusing on perioperative DEX administration, but the sample sizes are relatively small and the conclusions vary. Thus, the evidence supporting its use in these patients is less than clear.

Therefore, this meta-analysis of RCT was conducted to investigate the role of DEX as an anesthetic adjuvant for perioperative hemodynamic control, its impact on opioid requirements, and possible adverse events in adult patients undergoing elective intracranial procedures.

2. Materials and methods

2.1. Search strategy and trial selection

This systematic review of RCT was performed according to the Preferred Reporting Items for Systematic Reviews and

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Meta-Analyses (PRISMA) guidelines [5]. Two researchers (K.P. and S.W.) independently searched the following databases in October 2013: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science. A basic search was performed using a combination of Medical Subject Headings ("dexmedetomidine" and "human") and free text words ("intracranial," "craniotomy," or "neurosurgery"). All searches were performed without language or publication date restrictions, and the results were collated and deduplicated in Endnote X7 (Thomson Reuters, New York, NY, USA). The titles and abstracts of potentially relevant studies were screened before retrieval of the full articles. Any controversy concerning study selection or data extraction was resolved by consensus with a third reviewer (F.J.). All three authors read the full papers and determined inclusion or exclusion.

2.2. Inclusion and exclusion criteria

To be eligible for this meta-analysis, publications had to meet the following four inclusion criteria: (1) original research comparing the preoperative or intraoperative intravenous administration of DEX with a placebo or opioids for elective intracranial procedures in adult patients under general anesthesia; (2) RCT study design; (3) provide at least one of the following outcome measures: hemodynamic variables, neuroendocrine responses, recovery characteristics, anesthetic and analgesic requirements, postoperative pain, adverse events (hypertension/hypotension, tachycardia/bradycardia, nausea, vomiting, shivering, prolonged sedation), antiemetic requirements, duration of the Postanesthesia Care Unit stay, hospital stay, or mortality; and (4) availability of full text.

2.3. Data extraction and quality assessment

All relevant data from the included studies were extracted and tabulated by two researchers (K.P. and S.W.). The following data were extracted: author, year of publication, sample size, and intervention measures. Corresponding authors were contacted for missing data when necessary. If trials investigated different DEX doses, only the outcomes after the highest DEX dose administration were extracted [6].

Validity was assessed and scored by two researchers (S.W. and H.L.) and checked by a third author (F.J.) using a modified 7 point, 4 item Oxford scale [7,8], which considered the reporting and adequacy of randomization (2 points), allocation concealment (1 point), double blinding (2 points), and description of drop-outs (2 points).

2.4. Statistical analysis

When outcomes of interest were reported by two or more studies, included articles were pooled and weighted using Review Manager (version 5.1, 2011; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Categorical outcomes are reported as the risk ratio (RR) and 95% confidence interval (CI), while continuous outcomes are reported as the weighted mean difference (MD). A p value < 0.05 was used to determine statistical significance. Heterogeneity was evaluated with the I^2 test. For outcome data with low heterogeneity ($I^2 \leqslant 30\%$), a fixed-effect model was used [6]. For outcome data with high heterogeneity ($I^2 > 30\%$), a random-effect model was selected.

Several sensitivity analyses were performed to further test the robustness of the results: (1) whether the model of the statistical method (random-effect *versus* fixed-effect model) would change the results; (2) whether the quality of publication (high quality or low quality studies) could influence the results of the meta-analysis; and (3) subgroup analysis was performed according to different criteria.

3. Results

3.1. Included studies

A total of 655 articles were relevant to the search terms. After screening of titles and abstracts, 19 studies were identified as being potentially eligible for inclusion. After reading the full-text articles, eight RCT involving 389 participants were finally included into this meta-analysis [9–16]. The flow diagram for the selection of RCT is shown in Figure 1.

3.2. Description of included trials

Table 1 presents details of the included trials. They investigated patients undergoing intracranial surgery of different types (resection of brain tumors, intracranial vascular lesions, or epileptic foci, and clipping of cerebral aneurysms). All participants were adults with an American Society of Anesthesiologists (ASA) classification of I to III.

Six RCT compared the preoperative or intraoperative intravenous administration of DEX with a placebo [9–11,14–16], and two RCT compared DEX with an opioid (remifentanil) [12,13]. The DEX administration scheme varied between the included trials: all RCT applied DEX as a bolus (0.5–1 μg/kg), whereas the most common dose was 1 μg/kg; and six RCT used a combination of a DEX bolus with subsequent continuous infusion (0.2–1 μg/kg/hour) until the end of surgery. Six trials administered a balanced inhalational general anesthesia using sevoflurane or isoflurane. Total intravenous anesthesia with propofol was used in one trial, and sevoflurane was combined with propofol in another trial.

3.3. Methodological quality

The quality assessment of included RCT is presented in Table 1. The median quality score of data reporting was 4 (range, 2–7). All included trials were randomized and double-blinded. Three studies detailed the methods of randomization, and four studies detailed the methods of double-blinding. Only two studies clearly reported allocation concealment.

3.4. DEX versus placebo for intraoperative BP and heart rate control

Four trials including 172 patients compared intraoperative pharmacological intervention to control BP or heart rate (HR) in patients treated with DEX or placebo [11,14–16]. Meta-analysis showed that a significantly lower incidence of treatment for hypertension and hypotension was associated with DEX (RR = 0.48, 95% CI 0.31–0.75, $p = 0.001$; and RR = 0.66, 95% CI 0.43–1.01, $p = 0.05$, respectively) (Fig. 2), whereas there was no significant difference in the incidence of treatment for tachycardia and bradycardia between the groups (RR = 0.70, 95% CI 0.28–1.73, $p = 0.44$; and RR = 0.75, 95% CI 0.18–3.10, $p = 0.69$, respectively) (Fig. 3). The fixed-effect model was selected, since there were no significant heterogeneities.

3.5. DEX versus placebo for mean arterial pressure and HR when extubated

Two trials including 70 patients compared extubation mean arterial pressure (MAP) in patients treated with DEX or placebo [10,11]. Meta-analysis showed that a significantly lower extubation MAP was associated with DEX (MD = −9.74 mmHg, 95% CI −12.35 to −7.12, $p < 0.00001$) (Fig. 4A). The fixed-effect model was selected.

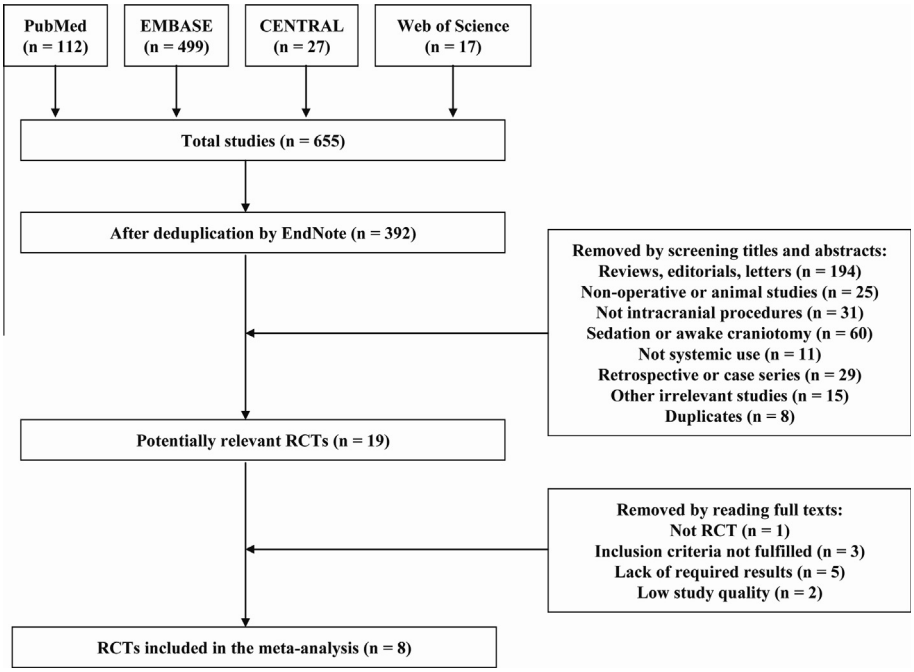

Fig. 1. Flow chart of retrieved, excluded, and eventually analyzed trials of dexmedetomidine as an anesthetic adjuvant for intracranial procedures. RCT = randomized controlled trial.

Table 1
Study characteristics of trials included in the meta-analysis of dexmedetomidine as an anesthetic adjuvant for intracranial procedures

Study [ref]	Intervention time	Dosing scheme (number of patients)	Type of surgery	Anesthesia	Quality score[a]
Tanskanen 2006 [16]	Loading dose before induction, maintenance until the start of skin closure	1. Dexmedetomidine 0.2 ng/mL (17) 2. Dexmedetomidine 0.4 ng/mL (18) 3. Placebo (18)	Resection of supratentorial tumor	Nitrous oxide + isoflurane	2/1/2/2
Bekker 2008 [15]	Loading dose after intubation, maintenance until 20 minutes before the end of surgery	1. Dexmedetomidine 1 μg/kg + 0.5 μg/kg/hour (28) 2. Placebo (28)	Resection of brain tumor, intracranial vascular lesion, or epileptic focus	Sevoflurane	1/0/2/2
Uyar 2008 [14]	A single bolus dose 10 minutes before induction	1. Dexmedetomidine 1 μg/kg (20) 2. Placebo (20)	Resection of supratentorial tumor or clipping of cerebral aneurysm	Nitrous oxide + isoflurane	2/0/2/0
Turgut 2009 [12]	Loading dose before induction, maintenance until the end of surgery	1. Dexmedetomidine 1 μg/kg + 0.2–1 μg/kg/hour (25) 2. Remifentanil 1 μg/kg + 0.05–1 μg/kg/minute (25)	Supratentorial craniotomy	Propofol	2/1/2/0
Gunduz 2009 [13]	Loading dose before induction, maintenance until the start of skin closure	1. Dexmedetomidine 0.5 μg/kg + 0.6 μg/kg/hour (40) 2. Remifentanil 0.5 μg/kg + 0.25 μg/kg/minute (40)	Intracranial surgery (vascular or space-occupying lesion)	Sevoflurane	1/0/1/0
Soliman 2011 [11]	Loading dose before induction, maintenance until the end of surgery	1. Dexmedetomidine 1 μg/kg + 0.4 μg/kg/hour (20) 2. Placebo (20)	Resection of supratentorial tumor	Sevoflurane	1/0/1/0
Gu 2012 [10]	A single bolus dose 10 minutes before the end of surgery	1. Dexmedetomidine 0.5 μg/kg (15) 2. Placebo (15)	Clipping of cerebral aneurysm	Sevoflurane + propofol	1/0/1/0
Kaushal 2013 [9]	Loading dose before induction, maintenance until the end of surgery	1. Dexmedetomidine 1 μg/kg + 0.4 μg/kg/hour (20) 2. Placebo (20)	Resection of intracranial tumor	Nitrous oxide + isoflurane	1/0/1/0

[a] Quality mark included assessment of reporting and adequacy of randomization (2 points), allocation concealment (1 point), double blinding (2 points), and description of drop-outs (2 points).
ref = reference.

Three trials including 110 patients compared extubation HR in patients treated with DEX or placebo [9–11]. Meta-analysis showed that a significantly lower extubation HR was associated with DEX (MD = −16.35 beats/minute, 95% CI −20.00 to −12.70, $p < 0.00001$) (Fig. 4B). However, there was significant heterogeneity.

3.6. DEX versus placebo for postoperative BP and HR control

Two trials including 86 patients compared postoperative pharmacological intervention to control BP in patients treated with DEX or placebo [10,15], and three trials including 122 patients compared postoperative intervention for HR control [10,15,16].

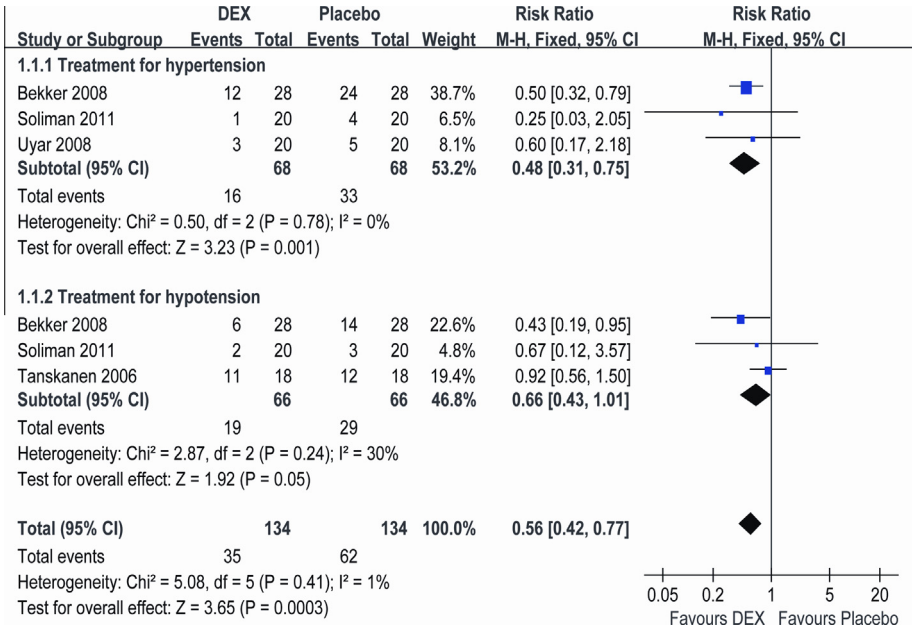

Fig. 2. Meta-analysis of intraoperative blood pressure control in patients treated with dexmedetomidine *versus* placebo. CI = confidence interval, DEX = dexmedetomidine, df = degrees of freedom, M-H = Mantel-Haenszel. (This figure is available in colour at www.sciencedirect.com.)

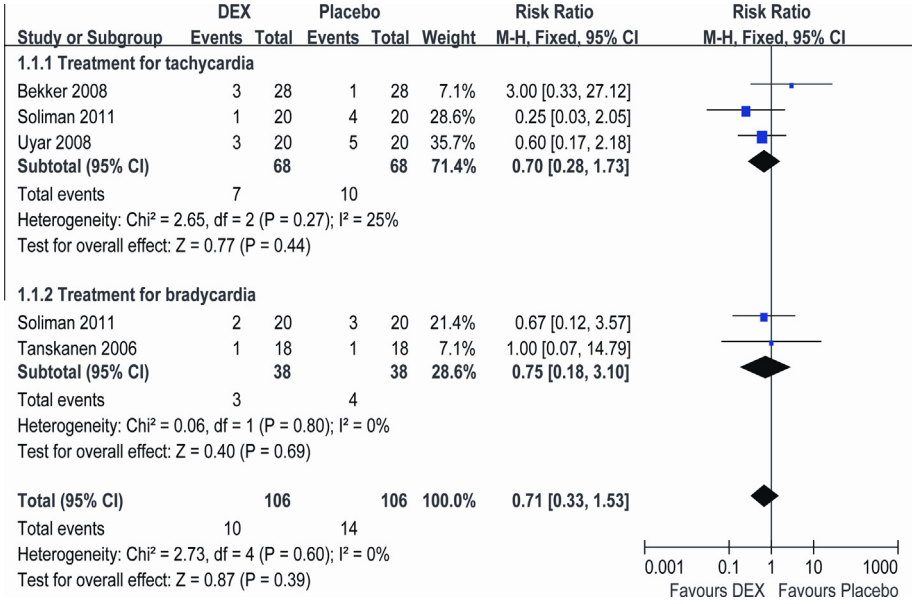

Fig. 3. Meta-analysis of intraoperative heart rate control in patients treated with dexmedetomidine *versus* placebo. CI = confidence interval, DEX = dexmedetomidine, df = degrees of freedom, M-H = Mantel-Haenszel. (This figure is available in colour at www.sciencedirect.com.)

Meta-analysis showed that a significantly lower incidence of treatment for postoperative hypertension and tachycardia was associated with DEX (RR = 0.37, 95% CI 0.17–0.79, $p = 0.01$; and RR = 0.14, 95% CI 0.03–0.59, $p = 0.007$, respectively), whereas there was no significant difference in the incidence of treatment for postoperative hypotension and bradycardia between the two groups (RR = 0.11, 95% CI 0.01–1.97, $p = 0.13$; and RR = 1.00, 95% CI 0.07–14.79, $p = 1.00$, respectively) (Fig. 5, 6). There were no significant heterogeneities, so the fixed-effect model was selected.

3.7. DEX versus placebo for extubation time

Four trials including 162 patients compared extubation time in patients treated with DEX or placebo [10,11,15,16]. Meta-analysis showed no significant difference between the two groups (MD = −12.09 minutes, 95% CI −25.81 to 1.63, $p = 0.08$) (Fig. 7A). The analysis was influenced by heterogeneity.

3.8. DEX versus placebo for intraoperative additional fentanyl requirements

Two trials including 92 patients compared intraoperative additional fentanyl requirements in patients treated with DEX or placebo [15,16]. Meta-analysis showed that significantly lower additional fentanyl requirements were associated with DEX (MD = −0.78 μg/kg, 95% CI −1.51 to −0.05, $p = 0.04$) (Fig. 7B). The fixed-effect model was selected.

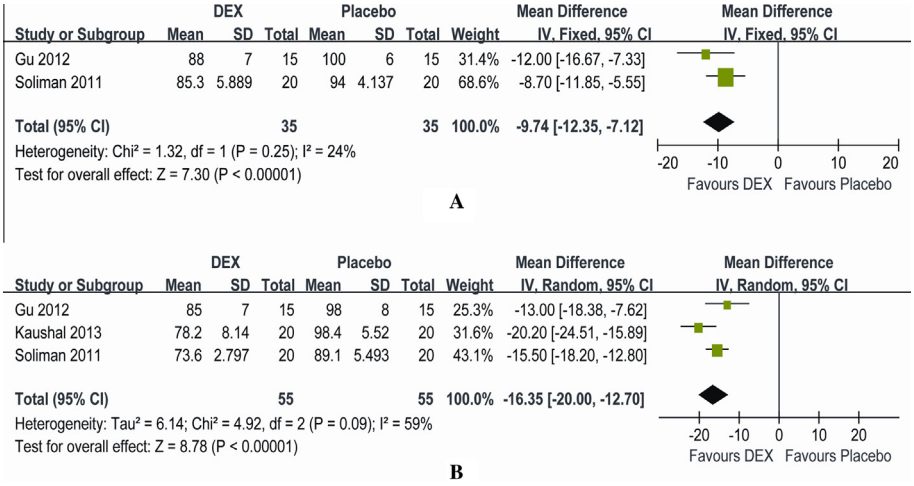

Fig. 4. Meta-analysis of (A) mean arterial pressure and (B) heart rate at extubation in patients treated with dexmedetomidine *versus* placebo. CI = confidence interval, DEX = dexmedetomidine, df = degrees of freedom, IV = Inverse Variance. (This figure is available in colour at www.sciencedirect.com.)

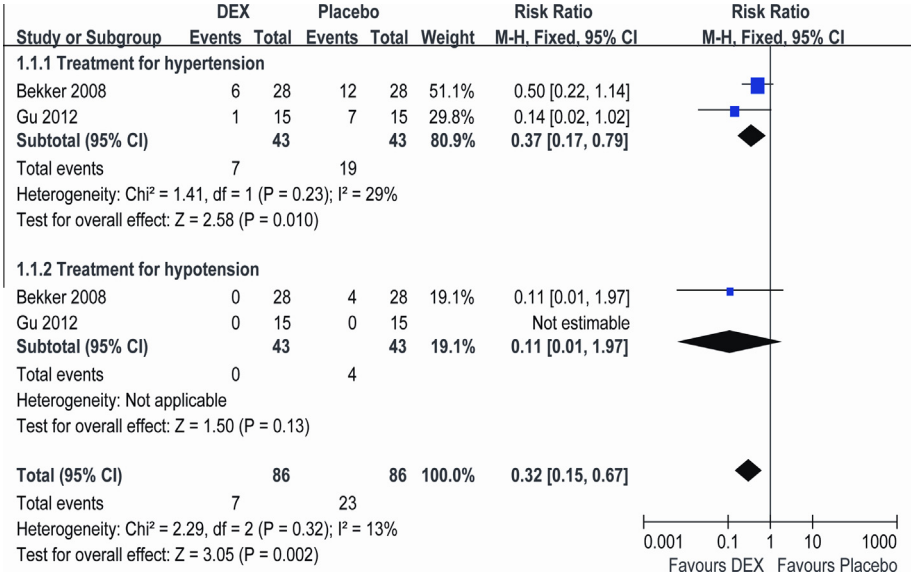

Fig. 5. Meta-analysis of postoperative blood pressure control in patients treated with dexmedetomidine *versus* placebo. CI = confidence interval, DEX = dexmedetomidine, df = degrees of freedom, M-H = Mantel-Haenszel. (This figure is available in colour at www.sciencedirect.com.)

3.9. DEX versus placebo for arterial partial pressure of carbon dioxide at 2 hours postoperatively

Two trials including 76 patients compared arterial partial pressure of carbon dioxide (P_aCO_2) at 2 hours postoperatively in patients treated with DEX or placebo [11,16]. There was no significant difference between the two groups (MD = −1.83 mmHg, 95% CI −5.02 to 1.36, $p = 0.26$) (Fig. 7C). The analysis was influenced by heterogeneity.

3.10. DEX versus placebo for postoperative antiemetic requests

Two trials including 96 patients compared postoperative antiemetic requests in patients treated with DEX or placebo [11,15]. Meta-analysis showed that a significantly lower incidence of postoperative antiemetic requests was associated with DEX (RR = 0.51, 95% CI 0.33–0.80, $p = 0.003$) (Fig. 7D). The fixed-effect model was selected, since there was no significant heterogeneity.

3.11. DEX versus remifentanil for intubation HR, skin incision HR, and extubation HR

Two trials including 130 patients compared HR at intubation, skin incision, and extubation in patients treated with DEX or remifentanil [12,13]. There was no significant difference between the two groups (MD = 1.25, 95% CI −9.40 to 11.90, $p = 0.82$; and MD = 4.77, 95% CI −13.81 to 23.35, $p = 0.61$; and MD = −3.30, 95% CI −23.98 to 17.38, $p = 0.75$, respectively). The analyses were influenced by heterogeneity.

3.12. DEX versus remifentanil for extubation time, response to verbal commands, and time to orientation

Two trials including 130 patients compared extubation time, response to verbal commands, and time to orientation in patients treated with DEX or remifentanil [12,13]. There was no significant difference between the groups (MD = 1.28, 95% CI −0.55 o 3.11, $p = 0.17$; and MD = 2.72, 95% CI −1.07 to 6.52, $p = 0.16$; and

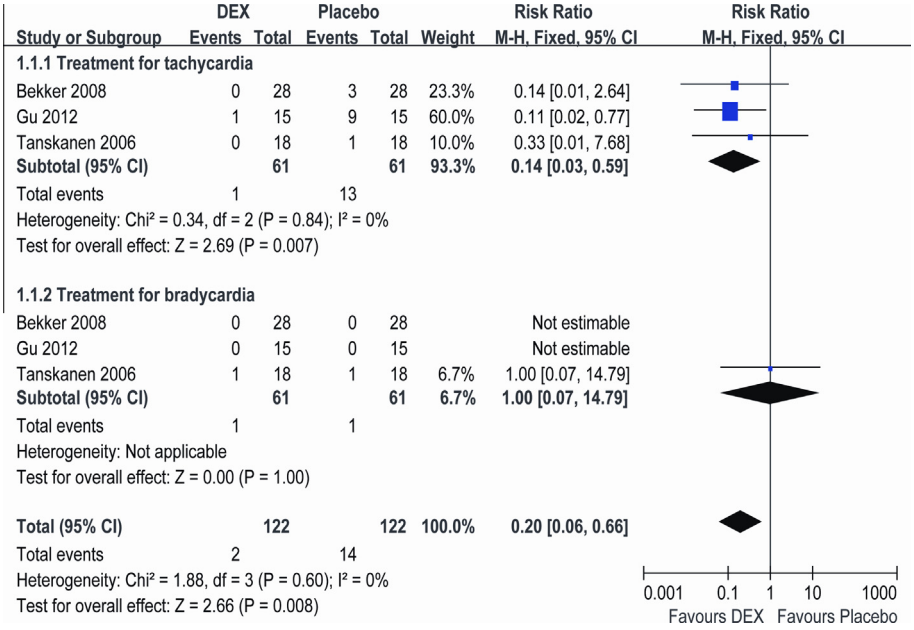

Fig. 6. Meta-analysis of postoperative heart rate control in patients treated with dexmedetomidine *versus* placebo. CI = confidence interval, DEX = dexmedetomidine, df = degrees of freedom, M-H = Mantel-Haenszel. (This figure is available in colour at www.sciencedirect.com.)

MD = 4.73, 95% CI −1.65 to 11.10, $p = 0.15$, respectively). The analyses were influenced by heterogeneity.

4. Discussion

The current meta-analysis revealed that patients treated with DEX compared with placebo needed significantly less intraoperative pharmacological intervention for hypertension and hypotension, and less postoperative treatment for hypertension and tachycardia. Patients also showed lower extubation MAP and HR, lower intraoperative additional fentanyl requirements, and fewer postoperative antiemetic requests associated with DEX. Moreover, DEX may not increase extubation time, the risk of perioperative bradycardia, or P_aCO_2 at 2 hours postoperatively.

Perioperative hemodynamic control for intracranial surgery patients is challenging, especially in those with hypertension. Hypertensive episodes during surgery may lead to catastrophic results [1]. Additionally, the manipulation of certain brain structures may cause cardiovascular changes. Opioids, anesthetics, and antihypertensive drugs are generally used to blunt hypertensive responses at several critical moments (such as intubation, pinning, incision, closure, and extubation). However, it may take a long time to treat acute hypertension and repeated doses may be administered. Subsequently, there is likely to be a period of hypotension due to overcompensation. As a result, patients might suffer from brain ischemia.

DEX has been widely used as an anesthetic adjuvant in various procedures. In adult patients, it is generally initiated with a loading infusion of 1 μg/kg over 10 minutes before induction, followed by a maintenance infusion of 0.2–1 μg/kg/hour until 20–30 minutes before the end of surgery. Its sympatholytic and antinociceptive properties are desirable for neurosurgical patients, so it could be used to improve hemodynamic stability at critical moments. The results of this meta-analysis demonstrated that patients treated with DEX compared with placebo needed less intraoperative intervention for both hypertension and hypotension, and less postoperative treatment for both hypertension and tachycardia. In addition, patients had lower MAP and HR when extubated. The better hemodynamic profile of DEX would help those patients with a history of cardiovascular disease to avoid potential perioperative complications such as myocardial ischemia and myocardial infarction.

Activation of the sympathetic nervous system is considered to be the final common pathway leading to perioperative hypertension. Uyar et al. [14] compared plasma cortisol, prolactin, and blood glucose levels after skull-pin insertion between DEX and placebo groups and found that DEX administration was significantly associated with lower values of these molecules. Olsen et al. [17] showed that the levels of catecholamines, aldosterone, renin, and endothelin after a craniotomy were higher in hypertensive patients. Other studies found that DEX decreased plasma epinephrine and norepinephrine levels perioperatively [18,19]. Thus, DEX could attenuate hypertensive responses associated with harmful surgical stimulation. However, there is not enough evidence to draw a systematic conclusion focusing on neuroendocrine responses because only one trial's results were included in this meta-analysis.

Opioids provide effective analgesia and prevent hemodynamic responses to stimulation. When used at high doses, however, they may cause delayed awakening, respiratory depression, increased intracranial pressure, and postoperative nausea and vomiting. DEX has been shown to effectively reduce opioid requirements and potentiate analgesia [6]. The current meta-analysis reported the same outcome: patients treated with DEX needed less intraoperative additional fentanyl. These results provide further evidence of the DEX-related improvement of hemodynamic stability. The difference in the amount of fentanyl needed is assumed to have been compensated for by DEX. Additionally, the anesthetic sparing effects of DEX are well known. It has been shown to reduce isoflurane requirements dose-dependently up to 90% [20–22]. However, this meta-analysis could not definitively show a reduction in inhalation anesthetic consumption due to limited data.

DEX has been proven to have minimal effects on respiration [23,24]. Craniotomy patients receiving perioperative DEX have better preserved respiratory drive after operation. Tanskanen et al. [16] found that there was a clear trend towards lower postoperative P_aCO_2 values at all time points in the DEX groups than in the placebo group, although the differences were not statistically

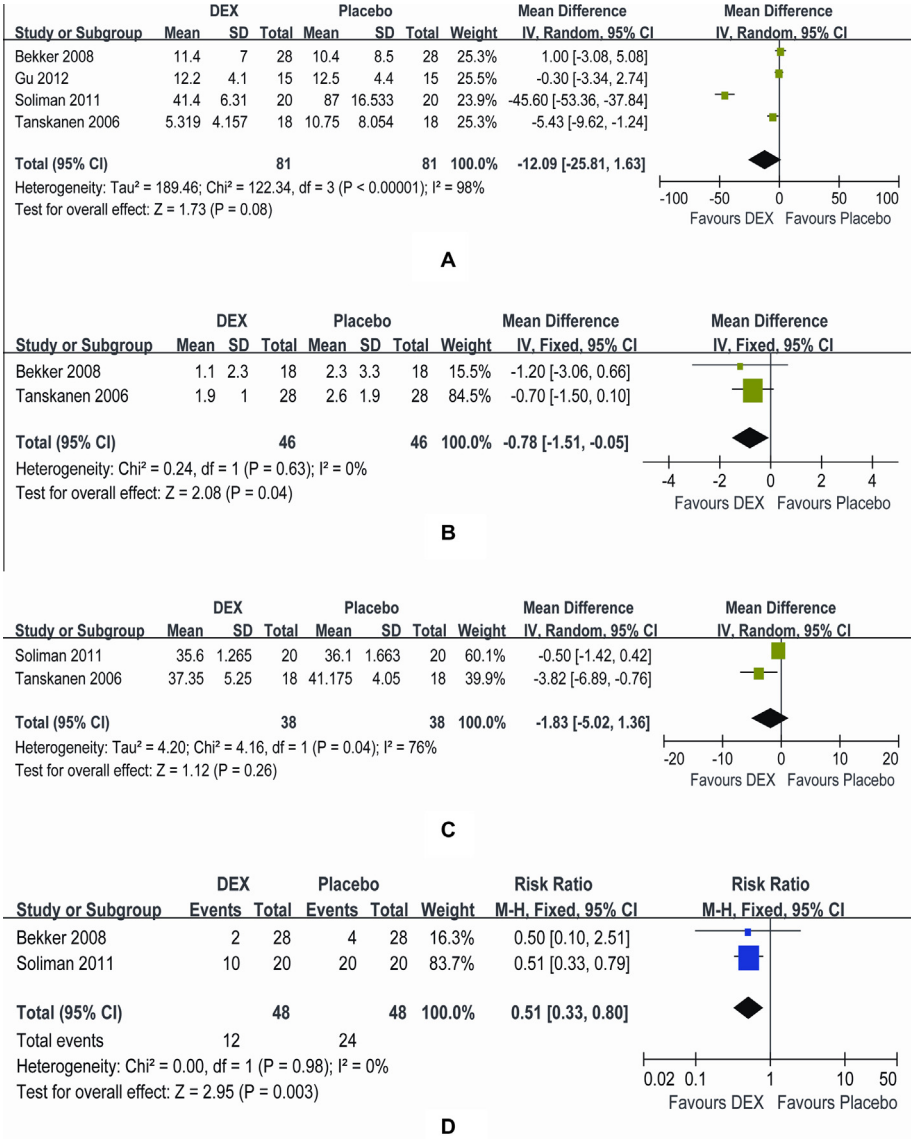

Fig. 7. Meta-analysis of (A) extubation time, (B) intraoperative additional fentanyl requirements, (C) P_aCO_2 at 2 hours postoperatively, and (D) postoperative antiemetic requests in patients treated with dexmedetomidine *versus* placebo. CI = confidence interval, DEX = dexmedetomidine, df = degrees of freedom, M-H = Mantel-Haenszel, IV = Inverse Variance. (This figure is available in colour at www.sciencedirect.com.)

significant. This meta-analysis showed no difference in postoperative P_aCO_2 values between the groups; however, the analysis was influenced by heterogeneity.

Craniotomy is associated with a high rate of postoperative nausea and vomiting [25,26]. This meta-analysis revealed that intraoperative DEX administration may decrease postoperative antiemetic requests, possibly as a result of the DEX-related improvement of hemodynamic stability and less opioid consumption.

The most common adverse event associated with DEX treatment is bradycardia [27]. The hemodynamic effects of DEX are well known (there is a higher risk for bradycardia if patients receive a fast bolus, while there is a lower risk if they receive a continuous infusion) [28,29]. This meta-analysis showed that the incidence of perioperative bradycardia with the need for active treatment was not significantly different between the DEX and placebo groups. A possible explanation is that patients included in this meta-analysis received a relatively lower bolus dose that was followed by a continuous infusion. Nevertheless, a recently published editorial stated that DEX administration might increase the risk of hypotension-related severe adverse events, such as stroke or myocardial infarction [30]. Therefore, caution in at risk patients is warranted.

This meta-analysis also reported data on the comparison of intraoperative DEX *versus* remifentanil administration. Remifentanil is an ultrashort-acting opioid and a suitable agent for use in neuroanesthesia [31–34]. However, only two trials focusing on perioperative hemodynamics and recovery profiles were included, and the analyses were influenced by heterogeneities. Thus, the evidence for this comparison is currently less clear and requires further research.

There were some limitations in this meta-analysis. First, all eight RCT had a relatively small sample size and the methodological quality was variable, although all trials were double-blinded. Second, there were significant heterogeneities in some analyses (extubation HR, extubation time, inhalation concentration, and P_aCO_2); therefore, the results should be assessed with caution. Third, publication bias might affect the precision of some outcomes, because positive results are more likely to be published than negative ones; hence the results might be overestimated. Fourth, it included only short-term outcomes focusing on

perioperative measurements such as hemodynamic variables, opioid and anesthetic consumption, and recovery parameters. Although all conclusions were clinically relevant, there was a lack of long-term follow-up data to observe possible neuroprotective effects of DEX and morbidity and mortality in this study. Larger outcome studies on long-term effects of intraoperative DEX in neurosurgical patients are warranted.

5. Conclusions

Only a small number of RCT were available, but the meta-analysis results show evidence that DEX is a safe and efficacious anesthetic adjuvant in intracranial procedures. Intraoperative DEX infusion improves perioperative hemodynamic control, decreases hemodynamic responses, and attenuates the emergence from anesthesia. Less intraoperative opioid consumption and fewer postoperative antiemetic requests were also found in patients treated with DEX compared with placebo. In contrast, the comparison with remifentanil is currently less clear due to limited data. A multi-center and large sample RCT which has adequate power to look at long-term as well as short-term outcomes of intracranial surgery patients is required.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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