의학석사 학위논문

The effect of intravenous dexmedetomidine on hemodynamic response in patients undergoing skull-pin head-holder application during neurosurgery

– A meta-analysis of randomized controlled trials

신경외과 수술에서 두개골 핀 고정시 혈역학적 변화에 대한 덱스메데토미딘의 효과

–무작위 대조시험의 메타분석

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의학과 마취통증의학전공

전 수 영

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지도교수 김 진 희

이 논문을 의학석사 학위논문으로 제출함

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Abstract

The effects of intravenous dexmedetomidine on hemodynamic response in patients undergoing skull-pin head-holder application during neurosurgery – A meta-analysis of randomized controlled trials

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Objectives. Skull-pin head-holder application during neurosurgery is a highly noxious stimulus that may lead to abrupt hemodynamic change, which is an unfavorable response to maintain hemodynamics stability. The aim of this meta-analysis was to evaluate the effects of intravenous dexmedetomidine on

hemodynamic response (blood pressure and heart rate) resulting from the application of skull-pin head-holder in neurosurgery.

Methods. A systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. The protocol was registered with the International Prospective Register of Systematic Reviews (CRD 420119127876). Electronic databases were searched, without discrimination of publication year, language, and region, to identify all randomized controlled trials investigating the effects of dexmedetomidine on hemodynamic response resulting from skull-pin head-holder application during general anesthesia for neurosurgery. The mean arterial pressure and heart rate were analyzed using random-effect model, and the mean difference (MD) was calculated.

Results. Seventeen trials were identified; a total of 878 patients were enrolled. The analysis indicated that dexmedetomidine infusion reduced the mean arterial pressure (MD -11.70, 95% confidence interval [CI] -16.33 to -7.07, $p < 0.00001$) and heart rate (MD -14.48, 95% CI -23.10 to -5.86, $p = 0.001$) during skull-pin head-holder application. Subgroup analysis showed that dexmedetomidine was superior to fentanyl for the attenuation of hemodynamic response. Dexmedetomidine infusion also reduced the incidence of hypertension, tachycardia and brain relaxation score.

Conclusion. The result of this analysis indicates that intraoperative dexmedetomidine administration could decrease the hemodynamic response

and provide hemodynamic stability during skull-pin head-holder application in neurosurgery.

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Keywords: Dexmedetomidine; Hemodynamic response; intracranial surgery; Neurosurgery; Skull-pin head-holder; Brain relaxation score

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Introduction

The application of skull-pin head-holder is necessary to fixate the head of patients for optimal surgical approach during neurosurgery. During the application process, the pins are inserted into the periosteum, yielding highly nociceptive stimulus, despite the general anesthesia [1]. This painful stimulus usually promotes sympathetic activity, inducing acute tachycardia or systemic hypertension, which could increase cerebral blood flow in patients with impaired autoregulation [2]. Subsequently, it may increase intracranial pressure and decrease cerebral perfusion pressure [3]. Impairment of cerebral homeostasis results in cerebral edema or cerebral ischemia. Therefore, it is important to maintain stable hemodynamics during skull fixation in patients undergoing craniotomy.

For the attenuation of hemodynamic response to nociceptive stimulus during skull fixation, many studies have investigated various interventions including regional techniques and pharmacologic treatments. However, regional techniques, including local anesthetic infiltration at the pin insertion site and scalp block, have shown the possibility of failure due to inaccurate infiltration site or inadequate anesthetic doses [4]. Pharmacologic approaches, such as opioid [5], beta-blocker [6], ketamine [4], gabapentine [7], clonidine [8], and thiopental [1] have shown varying success rate.

Dexmedetomidine, an alpha-2 agonist, has sedative, analgesic, and

sympatholytic effects without respiratory depression [9]. Dexmedetomidine has been reported to reduce the hemodynamic response from intraoperative stress [10, 11], and opioid consumption [12], and may reduce analgesic requirement in the intensive care unit [9]. Therefore, the aim of this meta-analysis was to evaluate the effect of dexmedetomidine on hemodynamic response from skull fixation via skull-pin head- holder in patients undergoing craniotomy.

Materials and methods

Search strategy

This systematic review and meta-analysis was performed according to the Preferred Items for Systematic Reviews and Meta Analyses (PRISMA) statement [13]. A predefined protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO : CRD 42019127876). We searched a variety of databases, including MEDLINE, EMBASE, CENTRAL, CINAHL, Scopus and Web of Science, to identify randomized controlled trials (RCTs) investigating the effects of dexmedetomidine on hemodynamic response from skull-pin application. The last search was conducted on January 9, 2020. MeSH terms and keywords, such as “craniotomy”, “neurosurgery”, “intracranial surgery”, “brain tumor”, “dexmedetomidine”, and “precedex” were used; each finding was combined with the Boolean operator: “AND” or “OR”. A detailed search strategy for each database is shown in Appendix 1.

Study selection

Relevant studies were selected by screening the titles and abstracts. Subsequently, the full-texts of relevant studies were evaluated for eligibility. Two investigators independently conducted the process, and the third investigator participated in the selection process in the vent of a disagreement. The inclusion criteria were (1) randomized controlled trials, (2) patients

undergoing craniotomy, (3) use of intravenous dexmedetomidine infusion, and (4) reported outcomes related with intraoperative hemodynamics. We excluded the studies that did not report hemodynamic outcomes.

Data extraction

Two investigators independently investigated and extracted the data from the original full-text of articles. The following data such as the first author, publication year, study design, publication language, number of patients, age, study drugs, drug dose regimen, any intervention just before skull fixation, anesthetics and intraoperative analgesics were retrieved. We used GetData Graph Digitizer 2.26 (http://www.getdata-graph-digitizer.com) to extract the mean and standard deviation if the data were reported only in a graph format. The primary outcome was defined as the mean arterial pressure (MAP) measured during skull pin application. Secondary outcomes included the heart rate (HR) during skull pin application, the incidence of intraoperative hemodynamic events (hypertension, hypotension, tachycardia and bradycardia) and brain relaxation score after opening the dura. The missing standard deviation of the value was imputed based on the following steps [14]: (1) standard deviation of value measured at different time-point, (2) standard deviation of systolic blood pressure at the same time-point, (3) standard deviation of systolic blood pressure at different time-points, (4) average standard deviation of value from other trials using the same intervention.

Quality assessment

Two investigators independently assessed the methodological quality using the Cochrane Risk of bias tool. Risk of bias (selection bias, performance bias, detection bias, attrition bias and reporting bias) was graded as low, unclear, or high. If there was disagreement between two investigators, decision was made by discussion or with the third investigator.

Data synthesis and statistical analysis

The meta-analysis was performed using Revman 5.3 software (Cochrane Collaboration, Oxford, UK). Since the pre-defined outcomes were continuous variables, we calculated the mean difference (MD) with 95% confidence intervals. We planned to construct a forest plot using a random effect model. We also performed a subgroup analysis according to the control group: (1) dexmedetomidine vs. other analgesics and (2) dexmedetomidine vs. normal saline. Heterogeneity among the included studies was assessed using an I^2 statistic. Heterogeneity was graded as low ($0 < I^2 < 50\%$), moderate ($50\% \leq I^2 < 75\%$) or high ($I^2 \geq 75\%$).

Results

Characteristics of included studies

A total of 837 articles were acquired from literature search; of these, 357 articles were removed due to duplicated retrieval. Among the remaining articles, 455 articles were identified as irrelevant studies based on the titles (n = 417) and abstracts (n = 38). Subsequently, 8 articles were excluded because they did not report the outcomes related with the present study (n=4), they were conference abstracts (n=2), or they focused on the postoperative periods (n=2) (Fig.1). Hence, 17 RCTs (n=878) were included in the final analysis [3, 15-30]. The characteristics of all included RCTs are shown in Table 1. The effect of dexmedetomidine was compared with placebo in 8 studies [3, 17-19, 24, 25, 27, 30], fentanyl in 6 studies [15, 16, 22, 23, 26, 28], remifentanil in 2 studies [20, 29], and propofol in one study [21].

Methodological assessment and Risk of bias

The risk of bias is summarized graphically in Fig. 2. All patients of the included studies were randomly allocated to one of two groups; however, six studies failed to describe the method of randomization. Most studies did not report the method of concealing the allocation process (14/17). In more than half of the included studies, it was clear that participants were unaware of their group assignment; however, it was unclear whether the assessors were blinded to group assignment. In most studies, the risk of attrition bias, reporting bias,

and other biases was regarded as low. Details for each risk of bias were described in Appendix 2.

Mean Arterial pressure

MAP was reported in 11 RCTs, including 576 patients (Fig. 3A) [15, 16, 19, 21-25, 28-30]. Blood pressure was measured continuously by arterial catheter in seven studies [15, 19, 21, 23-25, 30], whereas it was measured intermittently by non-invasive cuff in two studies [22, 28]. There were no descriptions how to measure blood pressure in another two studies.[16, 29] MAP during skull-pin application was lower in the dexmedetomidine group than in the control group (MD -11.70, 95% CI -16.33 to -7.07, $p < 0.00001$) and a high level of heterogeneity was found ($I^2 = 93\%$, $p < 0.00001$). In the subgroup analysis, the dexmedetomidine group showed a lower MAP than placebo group (MD -13.06, 95% CI -20.85 to -5.26, $p = 0.001$, $I^2 = 83\%$) and the fentanyl group (MD -16.65, 95% CI -20.05 to -13.25, $p < 0.00001$, $I^2 = 65\%$). However, there were no significantly differences in MAP in the dexmedetomidine group compared to the remifentanil group (MD 2.48, 95% CI -3.64 to 8.60, $p = 0.43$) and the propofol group (MD 5.90, 95% CI -0.27 to 12.07, $p = 0.06$).

Heart rate

HR during skull-pin application was reported in 10 RCTs, including 526 patients (Fig. 3B) [15, 16, 19, 21, 23-25, 28-30]. HR during skull-pin application was also lower in the dexmedetomidine group than in the control group (MD -14.48, 95% CI -23.10 to -5.86, $p = 0.001$). A high level of

heterogeneity among the studies was found (I^2= 96%, p < 0.00001). In the subgroup analysis, the HR was lower in the dexmedetomidine group compared with both the placebo group (MD -20.54, 95% CI -29.95 to -11.14, p < 0.0001, I^2 = 88%) and fentanyl group (MD -16.62, 95% CI -26.94 to -6.29, p = 0.002, I^2 = 91%). However, the HR in the dexmedetomidine group was comparable to remifentanil group (MD -0.22, 95% CI -4.11 to 3.67, p = 0.91) and propofol group (MD 2.90 95% CI -5.19 to 10.99, p = 0.48).

Hypertension and hypotension

The incidence of intraoperative hypertension was reported in 11 RCTs, including 607 patients (Fig. 4A) [3, 15-18, 20, 21, 25, 26, 28, 30]. The incidence of hypertension was lower in the dexmedetomidine group than in the control group (Relative risk [RR] 0.47, 95% CI 0.28 to 0.78, p = 0.004). A moderate level of heterogeneity was found (I^2 = 58%, p = 0.009). In the subgroup analysis, intraoperative hypertension was observed less frequently in the dexmedetomidine group compared with placebo group (RR 0.38, 95% CI 0.21 to 0.69, p = 0.002, I^2 = 54%). However, hypertensive events in dexmedetomidine group were similar to those in fentanyl group (RR = 0.19, 95% CI 0.03 to 1.17, p = 0.07, I^2 = 61%), remifentanil group (RR 1.33, 95% CI 0.51 to 3.49, p =0.56), and propofol group (RR 0.78, 95% CI 0.32 to 1.88, p =0.58).

The incidence of intraoperative hypotension was reported in 12 RCTs, including 610 patients (Fig. 4B) [3, 16-18, 20-23, 26-28, 30]. There were no

significant differences in the incidence of hypotension between two groups in both overall analysis (RR 1.07, 95% CI 0.72 to 1.58, p = 0.74, I^2 = 24%) and subgroup analysis (vs placebo: RR 0.82, 95% CI 0.47 to 1.40, p = 0.46, I^2 = 36%; vs fentanyl: RR 1.51, 95% CI 0.80 to 2.84, p = 0.21, I^2 = 0%; vs remifentanil: RR 0.50, 95% CI 0.10 to 2.58, p = 0.41; vs propofol: RR 2.67, 95% CI 0.76 to 9.31, p = 0.12).

Tachycardia and Bradycardia

The incidence of tachycardia during surgery was reported in 7 RCTs, including 369 patients (Fig. 5A) [3, 15, 16, 18, 25, 28, 30]. Tachycardia was significantly less frequent in the dexmedetomidine group than in the control group (RR 0.18, 95% CI 0.07 to 0.46, p = 0.0004) with low level of heterogeneity (I^2 = 24%, p = 0.25). Subgroup analyses showed that dexmedetomidine reduced intraoperative tachycardia compared to placebo (RR 0.22, 95% CI 0.06 to 0.76, p = 0.02, I^2 = 48%) and fentanyl (RR 0.08, 95% CI 0.01 to 0.62, p = 0.01, I^2 = 0%).

Intraoperative bradycardia was reported in 9 RCTs, including 450 patients (Fig. 5B) [3, 16, 18, 21-23, 27, 28, 30]. There were no significant differences in the incidence of bradycardia between two groups in both overall analysis (RR 1.49, 95% CI 0.72 to 3.11, p = 0.28, I^2 = 0%) and subgroup analysis (vs placebo: RR 1.81, 95% CI 0.29 to 11.32, p = 0.53, I^2 = 51%; vs fentanyl: RR 2.70, 95% CI 0.51 to 14.16, p = 0.24, I^2 = 0%; vs propofol: RR 1.20, 95% CI 0.40 to 3.61, p = 0.75).

Brain relaxation score

The brain relaxation score was assessed by a neurosurgeon in 5 RCTs [19, 20-23]; however, one of them reported only mean rank and sum of rank of brain relaxation scores which were incalculable to estimate pooled effect size [22]. Therefore, 4 RCTs were used to estimate the pooled effect size (Fig. 6) [19-21, 23]. The brain relaxation score was assessed on 3-, 4- or 5-points scales in each trials. It was divided as dichotomized outcomes: “low” (score 1) or “high” (score > 1). Low score means excellent, good, or no swelling, whereas high score means worsen, poor or swelling. The results of the present study indicated that dexmedetomidine could significantly decrease the incidence of high brain relaxation score (RR 0.50, 95% CI 0.28 to 0.89, $p = 0.02$, $I^2 = 44\%$)

Table 1. Baseline characteristics and population of the included randomized trials (n=17)

Author	Year	Design	Language	No. of patients (DEX/Control)	Study drug	Dose regimen (infusion)		Additional intervention just before skull fixation	Anesthetics	Intraoperative analgesics (bolus)
						DEX	Control			
Alagol	2006	RCT	Turkish	20/20	DEX/FTN	1 µg/kg/h followed by 0.5 µg/kg/h	1 µg/kg	-	Sevo (both group)	FTN (both group)
Batra	2017	RCT	English	25/25	DEX/FTN	0.4 µg/kg/h	4 µg/kg	-	Iso (both group)	FTN (both group)
Bekker	2008	RCT	English	28/28	DEX/placebo	1 µg/kg over 10 min followed by 0.5 µg/kg/h	-	-	Sevo + rFTN (both group)	FTN (both group)
Chakrabarti	2018	RCT	English	25/24	DEX/placebo	0.5 µg/kg/h	-	-	PPF+FTN (both group)	FTN (both group)
El Dawlatly	2006	RCT	English	14/14	DEX/placebo	0.25 µg/kg over 10 min	-	Group I/III : LA (1% lidocaine)	Sevo (both group)	-
Gunduz	2009	RCT	English	40/40	DEX/rFTN	0.5 µg/kg over 10 min followed by 0.6 µg/kg/h	0.25 µg/kg/min	-	DEX: Sevo + DEX rFTN: Sevo +rFTN	-
Gunes	2005	RCT	English	39/39	DEX/PPF	0.6-1.2 mg/kg/h	3-10 mg/kg/h	-	DEX: DEX + rFTN PPF: PPF + rFTN	-
Gupta	2017	RCT	English	25/25	DEX/FTN	1 µg/kg over 10 min followed by 0.04-0.05 µg/kg/min	3 µg/kg followed by 0.02-0.03 µg/kg/min	FTN 1 µg/kg i.v. with LA (2% lignocaine 3-5ml)	Iso (both group)	-
Ilhan	2010	RCT	English	15/15	DEX/FTN	1 µg/kg over 10 min followed by 0.4-0.5 µg/kg/min	4 µg/kg followed by 0.02-0.03 µg/kg/min	FTN 2 µg/kg i.v. with LA (2% lidocaine 3-5 ml)	Iso (both group)	FTN (both group)
Jadhav	2017	RCT	English	30/30	DEX/placebo	1 µg/kg over 10 min followed by 0.5 µg/kg/h	-	-	Iso (both group)	-
Kondavagilu	2017	RCT	English	60/30	DEX/placebo	1 µg/kg over 10 min or	-	LA (0.25% bupivacaine 2ml)	Iso (both group)	FTN (both group)

						0.5 μg/kg over 10 min				
Soliman	2011	RCT	English	20/20	DEX/placebo	1 μg/kg over 20 min followed by 0.4 μg/kg/h	-	-	Sevo (both group)	FTN (both group)
Srignesh	2019	RCT	English	12/12	DEX/FTN	0.5 μg/kg/h	1 μg/kg/h	Scalp block (0.25% bupivacaine + 1% lignocaine)	Iso (both group)	FTN (both group)
Tanskanen	2006	RCT	English	35/18	DEX/placebo	Plasma concentration of 0.2 or 0.4 ng/ml	-	FTN 2 or 4 μg/kg	Iso (both group)	FTN (both group)
Thongrong	2017	RCT	English	30/30	DEX/FTN	1 μg/kg over 10 min	1 μg/kg	-	Sevo (both group)	-
Turgut	2009	RCT	English	25/25	DEX/rFTN	1 μg/kg over 15 min followed by 0.2-1 μg/kg/h	1 μg/kg over 15 min followed by 0.05-1 μg/kg/min	-	DEX: PPF + DEX rFTN: PPF +rFTN	-
Uyar	2008	RCT	English	20/20	DEX/placebo	1 μg/kg over 10 min	-	FTN 1 μg/kg + lidocaine 1.5mg/kg i.v.	Iso (both group)	FTN (both group)

Age are expressed as the mean ± SD, RCT = randomized controlled trials, DEX = dexmedetomidine, FTN = fentanyl, rFTN = remifentanil, PPF = propofol, LA = local anesthetics, i.v.=intravenous administration, Sevo = sevoflurane, Iso = isoflurane

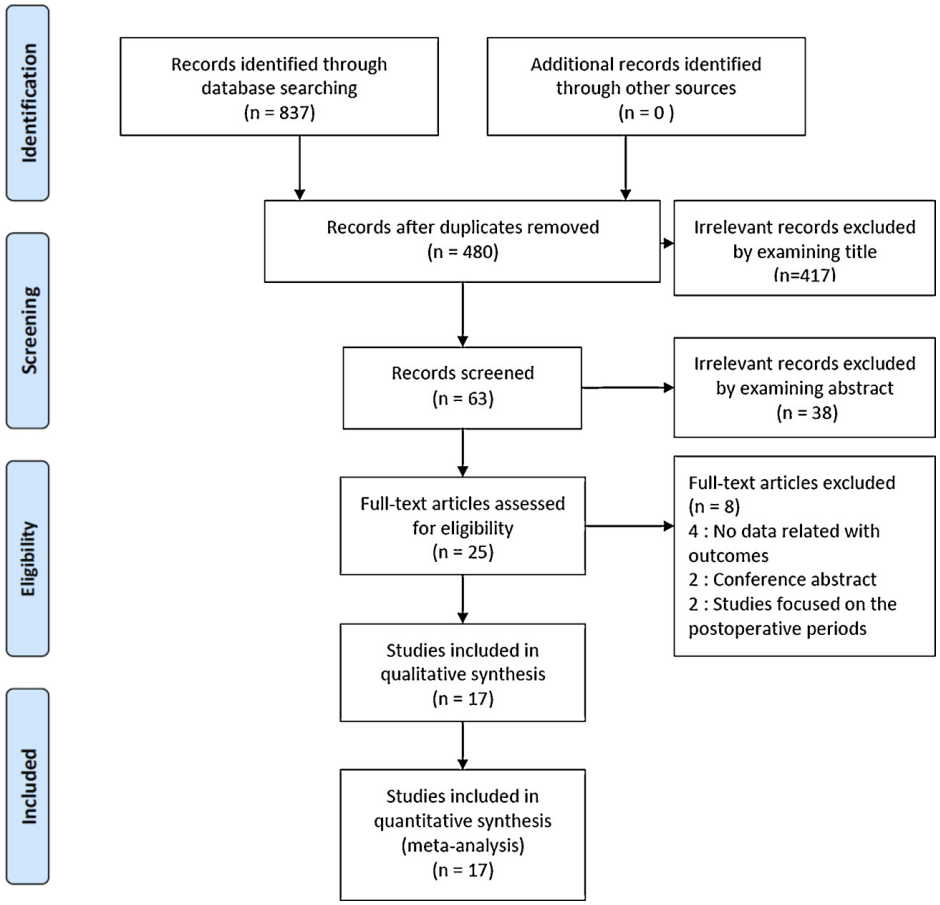


Figure 1. CONSORT diagram of included and excluded studies.

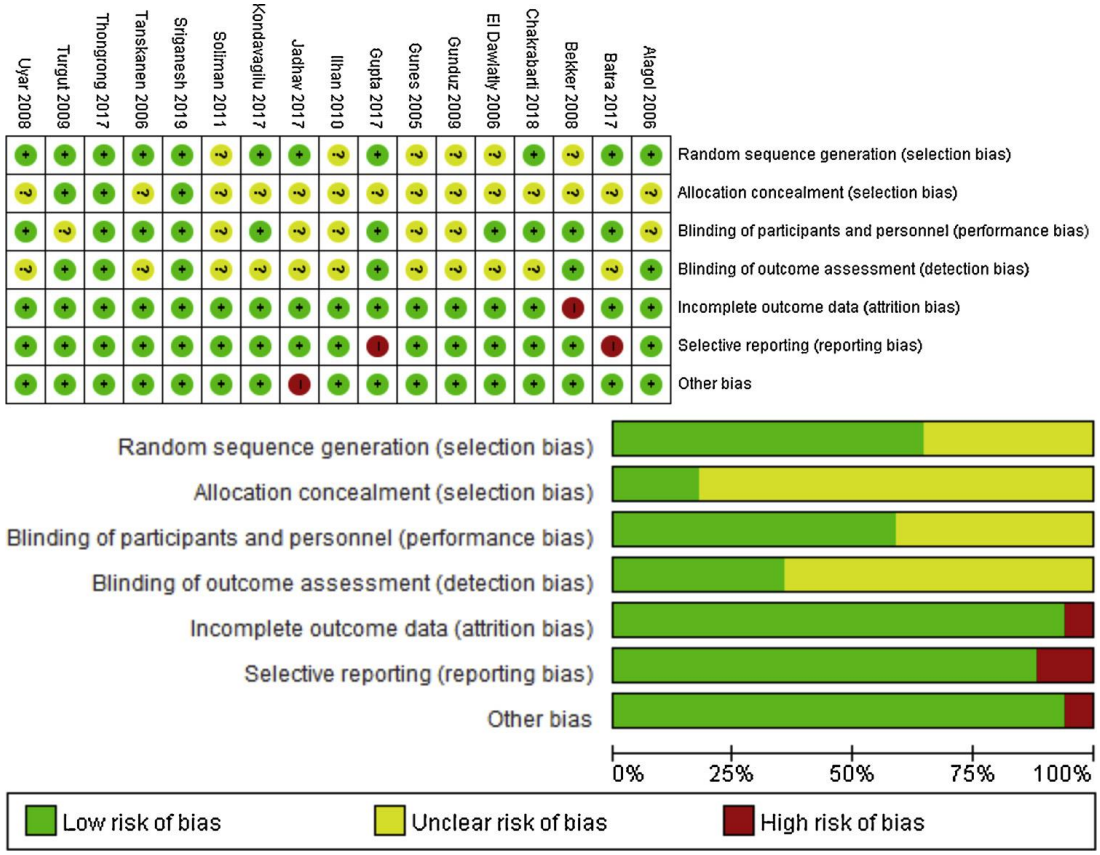
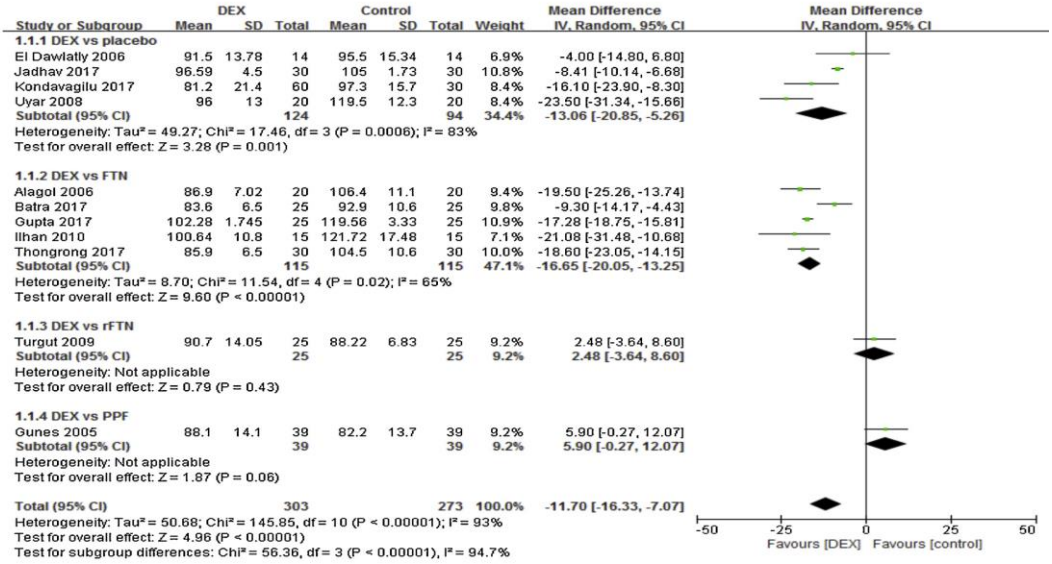


Figure 2. Risk of bias summary and graph.

(A)



(B)

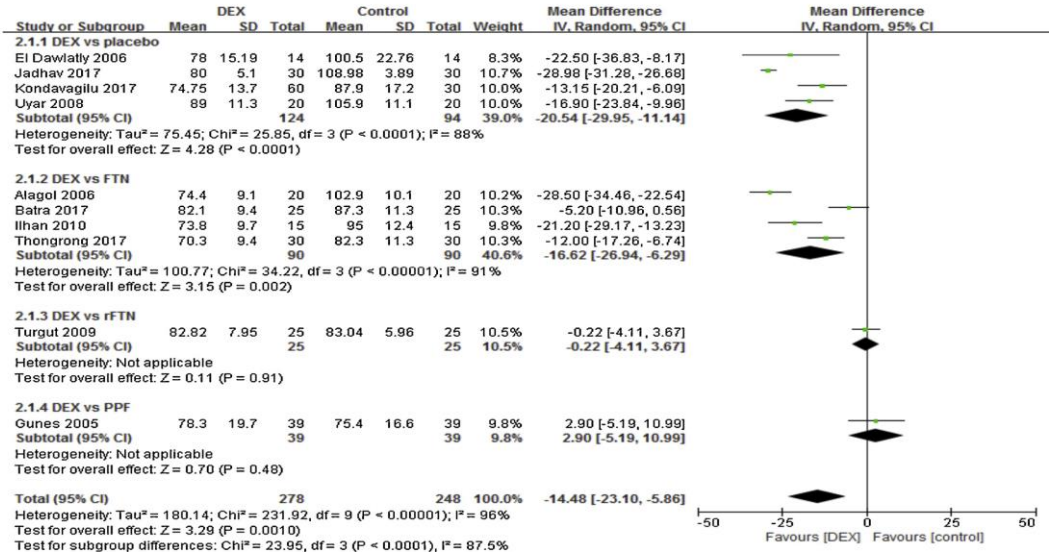


Figure 3. Forest plots for the hemodynamic variables during skull fixation: (A) mean arterial blood pressure (mmHg) and (B) heart rate (rates/min)

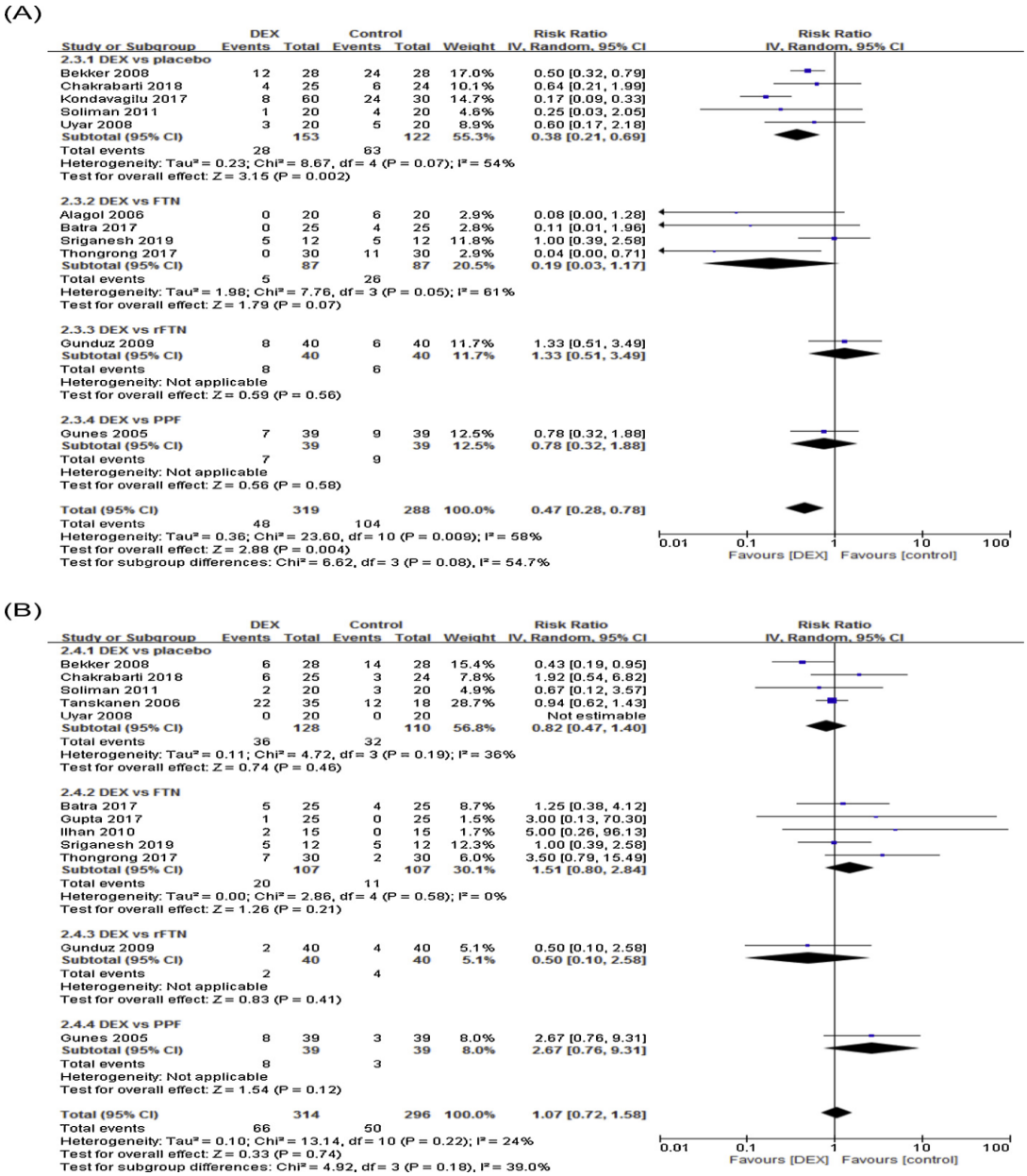
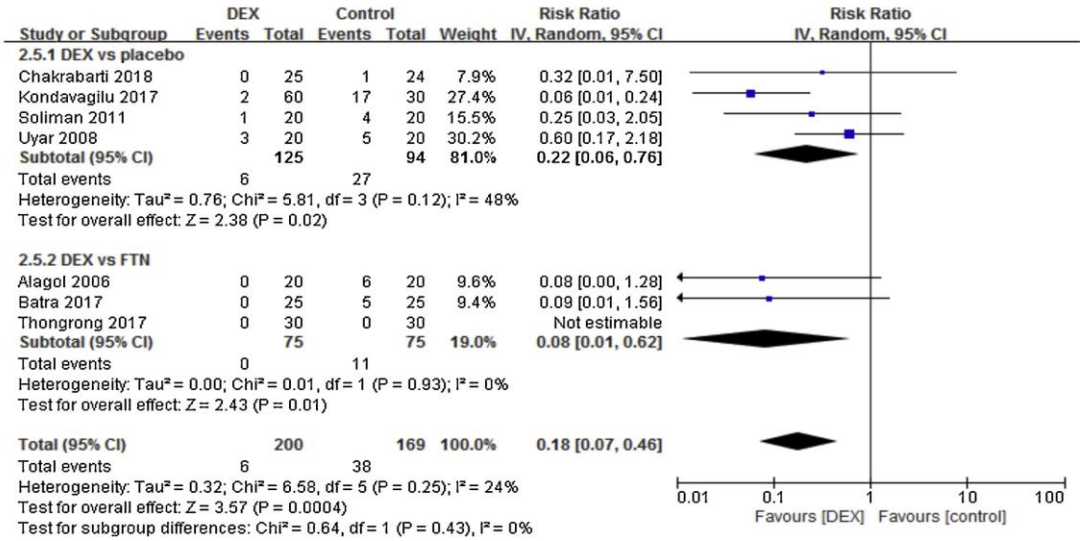


Figure 4. Forest plots for the hemodynamic events during surgery:

(A) hypertension and (B) hypotension

(A)



(B)

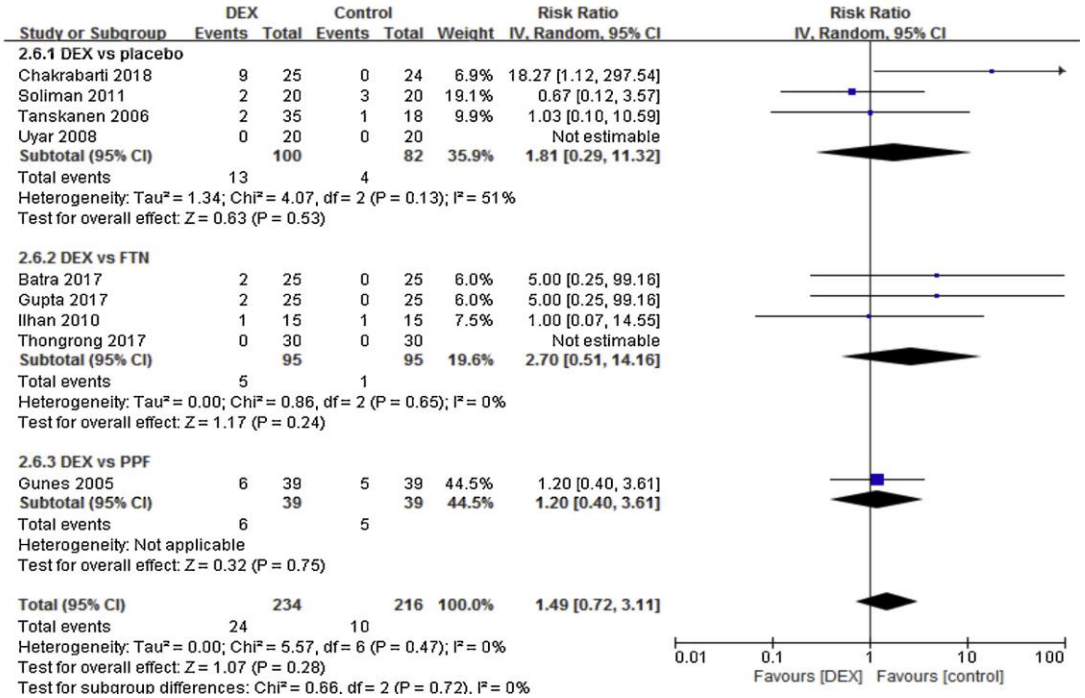


Figure 5. Forest plots for the hemodynamic events during surgery: (A) tachycardia and (B) bradycardia

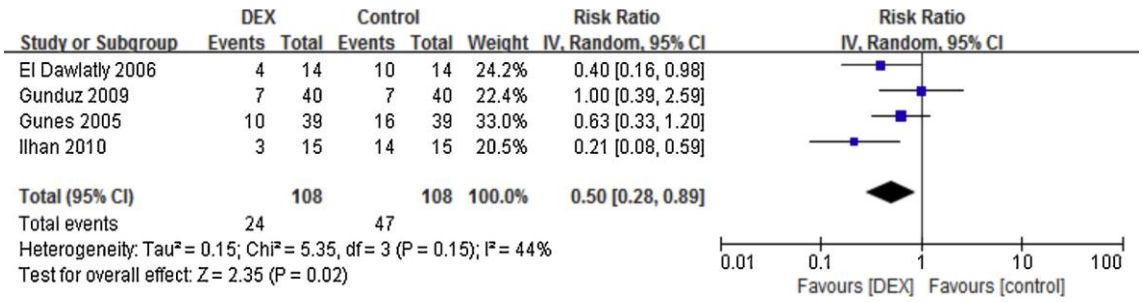


Figure 6. Forest plot for the brain relaxation score.

Discussion

The main finding of this study was that the use of dexmedetomidine may significantly reduce MAP and HR during the application of skull-pin head-holder. It also reduced the incidence of hypertension, tachycardia, and brain relaxation score intraoperatively. We found that dexmedetomidine attenuated the hemodynamic response from highly nociceptive stimulus. This finding is in agreement with previous studies which proved the preventive effect of dexmedetomidine on the hemodynamic response from intraoperative stressors, such as intubation [31, 32], extubation [33], pneumoperitoneum [34], and surgical incision [35].

In the subgroup analysis, patients in the dexmedetomidine group had greater hemodynamic stability than those in the fentanyl group during the skull-pin head-holder application process. This result correlates favorably well with previous study and supports the idea that dexmedetomidine provide great attenuation of intraoperative stress compared to fentanyl [36].

In addition to the MAP during the skull-pin head-holder application, the total incidence of hypertension and/or tachycardia was also evaluated during the surgery. The incidence of hypertension and/or tachycardia was significantly lower in the dexmedetomidine group than in the control group, which support the results of previous study [37].

The incidence of intraoperative hypotension was comparable between the two groups. Subgroup analysis also showed that the incidence of hypotension in the dexmedetomidine group was not higher than that in the control group (other anesthetics or normal saline). It is still controversial whether dexmedetomidine administration is associated with hypotension or not. Several authors reported dexmedetomidine-induced hypotension [38, 39, 40], whereas others insisted no significant differences in the incidence of hypotension between the dexmedetomidine group and the control group [41, 42]. According to the previous multivariate analysis [40], low MAP, high Acute Physiology and Chronic Health Evaluation (APACHE II) score, and history of coronary artery disease were independent factors for dexmedetomidine-induced hypotension. Given that our finding was based on RCTs including relatively healthy patients (American Society of Anesthesiologists class I-II or I-III), insignificant difference in the incidence of intraoperative hypotension between the two groups may be well explainable.

Brain relaxation means the firmness of the brain tissue during craniotomy and the degree of brain relaxation is an important aspect of neurosurgical conditions [43]. Brain relaxation score was significantly lower in the dexmedetomidine group, which can be explained by the decrease in cerebral blood flow caused by dexmedetomidine administration. This result may be interpreted as that dexmedetomidine infusion has favorable effect on brain relaxation. This is in line with the result of previous findings [22, 44], which

were excluded from this meta-analysis due to article type; a case series [44] and incalculable data (mean rank and sum of rank) [22].

There are several limitations in this study. First, the doses of dexmedetomidine were varied among the studies, which may result in a high level of heterogeneity among studies. Second, several studies conducted additional interventions such as local infiltration at the pin sites or opioid administration just prior to the skull-pin head-holder application [19, 22, 23, 25-27, 30], which may underestimate the effects of dexmedetomidine on hemodynamic response. Third, the pooled effect sizes of MAP and HR were estimated from the absolute values of hemodynamic parameters instead of the deviation from baseline. Most RCTs included in the present study report the absolute value of MAP and HR without the difference between the baseline and the skull fixation.

Conclusion

In conclusion, this meta-analysis supports the concept that intravenous dexmedetomidine attenuates hemodynamic response and provides hemodynamic stability during the skull-pin head-holder application in patients undergoing neurosurgery.

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Appendices

Appendix 1. Search strategy for each database.

Database	Order	Keywords	Results
MEDLINE	#1	Neurosurgery[MH] OR "neurosurgical procedures"[MH] OR neurosurgery[TIAB] OR craniotomy[MH] OR "brain tumor"[TIAB] OR "brain surgery"[TIAB] OR craniotomy[TIAB] OR "neurosurgical patient*"[TIAB] OR "intracranial surgery"[TIAB]	233981
	#2	dexmedetomidine[MH] OR dexmedetomidine[TIAB] OR precedex[TIAB]	5655
	#3	#1 AND #2	292
	#4	#3 AND HSSS(S)	143
EMBASE	#1	neurosurgery/exp OR neurosurgery:ab,ti OR craniotomy/exp OR craniotomy:ab,ti OR 'brain tumor':ab,ti OR 'brain surgery':ab,ti OR 'neurosurgical patient*':ab,ti OR 'intracranial surgery':ab,ti	316277
	#2	dexmedetomidine/exp OR dexmedetomidine:ab,ti OR Precedex:ab,ti	10767
	#3	#1 AND #2	563
	#4	'crossover procedure'/exp OR 'crossover procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'single blind procedure'/exp OR 'single blind procedure' OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer*	2517584

	#5	#3 AND #4	156
CENTRAL	#1	[mh neurosurgery] OR [mh "neurosurgical procedures"] OR [mh craniotomy] OR craniotomy:ti,ab,kw OR "neurosurgical patient*":ti,ab,kw OR neurosurgery:ti,ab,kw OR "brain tumor":ti,ab,kw OR "brain surgery":ti,ab,kw OR "intracranial surgery":ti,ab,kw	9165
	#2	[mh dexmedetomidine] OR dexmedetomidine:ti,ab,kw OR precedex:ti,ab,kw	4367
	#3	#1 AND #2	165
	#4	#3 AND Trials	164
CINHAL	S1	MH(craniotomy+) OR MH(neurosurgery+) OR (TI(neurosurgery) OR AB(neurosurgery)) OR (TI(craniotomy) OR AB(craniotomy)) OR (TI(neurosurgical patient*) OR AB(neurosurgical patient*)) OR (TI(brain tumor) OR AB(brain tumor)) OR (TI(brain surgery) OR AB(brain surgery)) OR (TI(intracranial surgery) OR AB(intracranial surgery))	8542
	S2	(TI(dexmedetomidine) OR AB(dexmedetomidine)) OR (TI(precedex) OR AB(precedex))	477
	S3	S1 AND S2	22
SCOPUS	#1	INDEXTERMS(neurosurgical procedures) OR INDEXTERMS(neurosurgery) OR INDEXTERMS(craniotomy) OR TITLE-ABS(neurosurgery) OR TITLE-ABS(craniotomy) OR TITLE-ABS(neurosurgical patient*) OR TITLE-ABS(brain tumor) OR TITLE-ABS(brain surgery) OR TITLE-ABS(intracranial surgery)	242750
	#2	INDEXTERMS(dexmedetomidine) OR TITLE-ABS(dexmedetomidine) OR TITLE-	9134

		ABS(precedex)	
	#3	#1 AND #2	451
	#4	(INDEXTERMS(randomized controlled trial) OR INDEXTERMS(controlled clinical trial) OR TITLE-ABS(randomized) OR TITLE-ABS(placebo) OR INDEXTERMS(drug therapy) OR TITLE-ABS(randomly) OR TITLE-ABS(trial) OR TITLE-ABS(groups)) AND NOT (INDEXTERMS(animals) AND NOT INDEXTERMS(humans))	9056489
	#5	#3 AND #4	193
Web of Science	#1	TS=(neurosurgery) OR TS=(craniotomy) OR TS=(brain tumor) OR TS=(brain surgery) OR TS=(neurosurgical patient*) OR TS=(intracranial surgery)	184089
	#2	TS=(dexmedetomidine OR precedex)	6864
	#3	#1 AND #2	349
	#4	TS=(clinical trial* OR research design OR comparative stud* OR evaluation stud* OR controlled trial* OR follow-up stud* OR prospective stud* OR random* OR placebo* OR “single blind*” OR double blind*)	4318533
	#5	#3 AND #4	159

Appendix 2. Details for judgement for each risk of bias for randomized controlled studies.

Study	Bias	Author's judgement	Reason for judgement
Alagol 2006	Random sequence generation (selection bias)	Low	The study and control groups were randomly determined by the envelope withdrawal method (translated)
	Allocation concealment (selection bias)	Unclear	There is no description.
	Blinding (performance)	Unclear	There is no description.
	Blinding (detection bias)	Low	The anesthetist who recorded the data was not informed about the contents of infusion solutions and iv bolus injectors (translated)
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.
Batra 2017	Random sequence generation (selection bias)	Low	Balanced randomization was done using random computer-generated table.
	Allocation concealment (selection bias)	Unclear	There is no description.
	Blinding (performance)	Low	Both the teams were blinded to the drugs by supplying prefilled syringes with same volume of normal saline and dexmedetomidine in saline.

	Blinding (detection bias)	Unclear	There is no description
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	High	Some predefined outcomes were not reported
	Other bias	Low	No other bias was detected.
Bekker 2008	Random sequence generation (selection bias)	Unclear	Patients were randomized to one of two groups but the methods were not described.
	Allocation concealment (selection bias)	Unclear	There is no description
	Blinding (performance)	Low	The anesthetic was managed by experienced neuro-anesthesiologists blinded to DEX or placebo regimen
	Blinding (detection bias)	Low	The intraoperative hemodynamic data obtained by machine.
	Incomplete outcome data (attrition bias)	High	Seventy two patients were recruited and two patients were removed. But outcomes were reported for 56 patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.
Chakrabarti 2018	Random sequence generation (selection bias)	Low	Randomization to the study group was performed at 1:1 ratio by a computer-generated random number table
	Allocation concealment	Unclear	There is no description

	(selection bias)		
	Blinding (performance)	Low	The attending anesthesiologist was blinded by providing fentanyl or premixed fentanyl and dexmedetomidine as colorless solutions in an unlabelled 50 mL syringe for constant infusion at 0.125 mL/kg/hour
	Blinding (detection bias)	Unclear	There is no description
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.
El Dawlatly 2006	Random sequence generation (selection bias)	Unclear	Patients were randomly allocated to groups but the methods were not described.
	Allocation concealment (selection bias)	Unclear	There is no description.
	Blinding (performance bias)	Low	Both the anesthetist who administered i.v. medications and the surgeon who performed local infiltration to the scalp were blinded to various treatment groups.
	Blinding (detection bias)	Unclear	There is no description.
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting	Low	Heart rate at pre-defined time point

	(reporting bias)		was not reported.
	Other bias	Low	No other bias was detected.
Gunduz 2009	Random sequence generation (selection bias)	Unclear	Patients were randomly allocated in 2 groups but the methods were not described.
	Allocation concealment (selection bias)	Unclear	There is no description.
	Blinding (performance bias)	Unclear	There is no description.
	Blinding (detection bias)	Unclear	There is no description.
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	Heart rate at pre-defined time point was not reported.
	Other bias	Low	No other bias was detected.
Gunes 2005	Random sequence generation (selection bias)	Unclear	Patients were randomly allocated in 2 groups but the methods were not described.
	Allocation concealment (selection bias)	Unclear	There is no description.
	Blinding (performance bias)	Unclear	There is no description.
	Blinding (detection bias)	Unclear	There is no description.
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.

	Selective reporting (reporting bias)	Low	Heart rate at pre-defined time point was not reported.
	Other bias	Low	No other bias was detected.
Gupta 2017	Random sequence generation (selection bias)	Low	Patients were randomized into two groups on the basis of computer generated random table.
	Allocation concealment (selection bias)	Unclear	There is no description.
	Blinding (performance bias)	Low	Our study was double blind in which the resident who was giving the drug was not aware about the drug and in postoperative care unit the sister on duty did the monitoring and recorded the results.
	Blinding (detection bias)	Low	Same as above
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	High	Heart rate at pre-defined time point was not reported.
	Other bias	Low	No other bias was detected.
Ilhan 2010	Random sequence generation (selection bias)	Unclear	The patients were randomized in two groups, but the method was not described.
	Allocation concealment (selection bias)	Unclear	There is no description.
	Blinding (performance bias)	Unclear	There is no description.

	Blinding (detection bias)	Unclear	There is no description.
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.
Jadhav 2017	Random sequence generation (selection bias)	Low	They were randomly divided into two groups by simple random sampling method
	Allocation concealment (selection bias)	Unclear	There is no description.
	Blinding (performance bias)	Unclear	There is no description.
	Blinding (detection bias)	Unclear	There is no description.
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	High	Our study is limited by small sample size and lack of comparative data in humans.
Kondavagilu 2017	Random sequence generation (selection bias)	Low	Patients were randomly allocated to one of the three groups using computer-generated table of random numbers.
	Allocation concealment	Unclear	There is no description.

	(selection bias)		
	Blinding (performance bias)	Low	Dexmedetomidine of different doses or placebo was diluted by an independent investigator. The test drug infusion was initiated by the attending anesthesiologist who was blinded to the test drug
	Blinding (detection bias)	Unclear	There is no description.
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.
Soliman 2011	Random sequence generation (selection bias)	Unclear	The patients were randomized in two groups, but the method was not described.
	Allocation concealment (selection bias)	Unclear	There is no description.
	Blinding (performance bias)	Unclear	There is no description.
	Blinding (detection bias)	Unclear	There is no description.
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.

Sriganesh 2019	Random sequence generation (selection bias)	Low	Randomisation was performed using a computer-generated random number table with 1:1 allocation ratio by an anaesthesiologist not directly involved in the trial or patient care
	Allocation concealment (selection bias)	Low	The group allocation list was discreetly shared with the anaesthesia technician (not involved in the intraoperative management)
	Blinding (performance bias)	Low	Both the study drugs were prepared in an identical 50 cc syringe as colourless solutions and provided to the operating room anaesthesiologist for administration to ensure blinding.
	Blinding (detection bias)	Low	Outcome assessor and the data analyst were blinded to the group allocation.
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.
Tanskanen 2006	Random sequence generation (selection bias)	Low	Balanced randomization using permuted blocks was applied.
	Allocation concealment (selection bias)	Unclear	There is no description
	Blinding (performance bias)	Low	In order to keep the investigators blind to the study treatment, the Hospital Pharmacy diluted DEX or placebo with sodium chloride solution 0.9% into a ready-to-use form.

	Blinding (detection bias)	Unclear	There is no description
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.
Thongrong 2017	Random sequence generation (selection bias)	Low	The random numbers were generated by computer
	Allocation concealment (selection bias)	Low	And concealed in sealed envelope.
	Blinding (performance bias)	Low	These study drugs were prepared by an anaesthetist nurse who was not involved in the study.
	Blinding (detection bias)	Low	Blood pressure, mean arterial pressure, and heart rate were recorded by a blinded anaesthesiologist.
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.
Turgut 2009	Random sequence generation (selection bias)	Low	The allocation was done by a computer-generated codes based on a two-way randomization
	Allocation concealment (selection bias)	Low	Kept in sequentially numbered envelops

	Blinding (performance bias)	Unclear	There is no description
	Blinding (detection bias)	Low	A blinded investigator assessed the outcomes
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients.
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.
Uyar 2008	Random sequence generation (selection bias)	Low	Patients were randomly allocated to one of 2 groups with the help of a computer-generated table of random numbers.
	Allocation concealment (selection bias)	Unclear	There is no description.
	Blinding (performance bias)	Low	DEX or placebo was diluted by one authors who was blinded to the recorded data
	Blinding (detection bias)	Unclear	There is no description.
	Incomplete outcome data (attrition bias)	Low	Outcomes were reported for all patients
	Selective reporting (reporting bias)	Low	All pre-specified and expected outcomes are reported.
	Other bias	Low	No other bias was detected.

국 문 초 록

연구 배경. 신경외과 수술에서 두개골 핀 고정은 갑작스러운 혈역학적 변화를 일으키는 매우 강력한 자극으로 알려져 있다. 이 메타분석의 목적은 신경외과 수술에서 두개골 핀 고정시 발생하는 혈역학적 변화(혈압 및 심박수)에 덱스메데토미딘 주입이 어떤 영향을 미치는지에 대한 효과를 평가하기 위한 것이다.

연구 방법. 전신마취 중 신경외과 수술에서 두개골 핀 고정시 혈역학적 변화에 미치는 덱스메데토미딘의 효과에 대한 무작위 대조시험을 대상으로 문헌검색을 하였다. PRISMA(Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 지침에 따라 체계적인 검토 및 메타 분석을 수행하였고 이 프로토콜은 International Prospective Register of Systematic Reviews(CRD 420119127876)에 등록되었다. 변량효과모형(random-effect models)을 사용하여 평균동맥압과 심박수를 분석하였고 평균차(mean difference, MD)를 계산하였다.

결과. 878명의 환자가 포함된 17개의 연구를 분석하였다. 두개골 핀 고정시 덱스메데토미딘 주입은 평균 동맥압을 평균차 −11.70, 95% 신뢰구간 −16.33 to −7.07, $p < 0.00001$, 심박수를 평균차 −14.48,

95% CI −23.10 to −5.86, p = 0.001만큼 감소시켰다. 하위집단(subgroup) 분석에서는 덱스메데토미딘이 펜타닐에 비해 혈역학적 반응을 완화시키는 것이 더 우수하였다. 또한 덱스메데토미딘은 고혈압, 빈맥, 뇌이완점수(brain relaxation score)를 감소시켰다.

결론. 신경외과 수술에서 두개골 핀 고정시 덱스메데토미딘 주입은 혈역학적 변화를 감소시켜 혈역학적 안정성을 제공할 수 있다.

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주요어: 덱스메데토미딘; 혈역학적 반응; 두개내 수술; 신경외과 수술; 두개골 핀 고정; 뇌이완점수

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