

Effect of Dexmedetomidine on Motor Evoked Potentials in the Adult Population: Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: Dexmedetomidine (DEX) is commonly used as an adjunct to total intravenous anesthesia (TIVA) to help reduce intraoperative consumption of propofol and opioids. However, the effect of DEX on transcranial motor-evoked potential (TCeMEPs) monitoring has remained controversial due to the covariances of dosage used, the presence of initial bolus, patient population, and duration of anesthesia. This systematic review and meta-analysis aimed to evaluate the effect of DEX on TCeMEPs amplitude in the adult population by analyzing different DEX dosage infusion groups interacting with different covariances.

METHODS: This systematic review consisted of meta-analyses of the literature from PubMed, Google Scholar, Science Direct, Springer, and some other sources to quantify the effect of DEX on TCeMEP amplitude. The total cohort consisted of 402 patients who underwent surgery with intraoperative TCeMEP monitoring and used DEX as an adjunct. For each study selected, various factors were collected, such as the dosage of DEX, the presence of initial bolus, TIVA regime, sample size, TCeMEPs amplitude at baseline and after DEX infusion, and the time when amplitudes were obtained. For the studies that did not report the amplitude of TCeMEPs, the number of times when TCeMEPs were lost during surgery was recorded. After data was extracted from the included studies, the effect size was investigated using a random effects model. Cochran Q test was used to evaluate the heterogeneity of studies and subgroups.

RESULTS: A significant small effect of 0.1-0.6 $\mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion on TCeMEPs amplitude with minimal heterogeneity, Cohen's $d = -0.30$, $p < .10$, $\tau^2 = .05$, $I^2 = 0.39$. A significant medium effect of DEX loading dose on TCeMEPs amplitude, Cohen's $d = -0.69$, $p = .01$. An overall high heterogeneity between the subgroups of patients with propofol-fentanyl and propofol-remifentanyl regime, $\tau^2 = .25$, $I^2 = 0.75$. After investigating individual studies that did not report the recordings of TCeMEPs, their findings are consistent with our results.

CONCLUSION: This study showed that a low dosage of DEX infusion (0.1-0.6 $\mu\text{g kg}^{-1} \text{h}^{-1}$) alone without initial bolus can be considered as a TIVA adjunct. Covariances, such as the presence of loading dose, the use of fentanyl, or the time when amplitude is collected, may lead to variation in the effect of DEX infusion on TCeMEPs amplitude.

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INTRODUCTION

Motor-evoked potential (MEP) is one of the intraoperative neurophysiology monitoring (IONM) techniques widely used during surgeries to help provide real-time feedback on a patient's motor tract function and prevent spinal cord or spinal nerve injury. MEP is the electrical signal elicited by the stimulation of the motor cortex, either by direct cortical stimulation (DCS-MEPs) or transcranial electrical stimulation (TCeMEPs). The monitoring of motor pathways by TCeMEPs is mainly used for spine surgeries that do not require an exposed cortex. They have a high sensitivity and specificity that can go up to 100%, but they are susceptible to many anesthetic agents and neuromuscular blockades (Biscevic et al., 2020; Legatt et al., 2016). Total intravenous anesthesia (TIVA) with propofol is commonly used for surgeries that undergo TCeMEP monitoring (Legatt et al., 2016).

However, previous studies showed that using dexmedetomidine (DEX) as an adjunct can help reduce intraoperative consumption of propofol and opioids, maintain intraoperative hemodynamic stability, and satisfy analgesic requirements with negligible respiratory depression (Bala et al., 2008; Li et al., 2015). Limited studies investigate the effect of DEX on MEP, and the results are controversial due to the covariances of dosage used, the presence of loading dose, patient population, and duration of anesthesia. Due to the possibility of MEP changes, including irreversible changes and loss of signal, it is crucial to conduct this study, which would allow a better understanding by considering different variances associated with the effect of DEX on MEP amplitude.

We performed a systematic review and meta-analysis to evaluate the effect of DEX on TCeMEP amplitude in an adult population by analyzing data extracted from previous studies. This study investigates whether significant MEP changes can be seen among different DEX dosages. This review also estimates how a DEX loading dose before infusion can affect the MEP amplitude for secondary analysis. A tertiary subgroup analysis was also performed to evaluate how the combination of propofol-fentanyl interacting with DEX can affect MEP amplitude.

METHODS

Protocol

This review utilized the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) procedure. The flow diagram for the PRISMA procedure is included (Fig. 1).

Study Search and Eligibility

PubMed, Google Scholar, Science Direct, and Springer were searched for cohort studies with keywords such as dexmedetomidine, TCeMEPs/transcranial motor-evoked potential, IONM/IOM, amplitude, surgery, etc.

The following inclusion criteria were established before database search: (1) studies conducted in patients undergoing surgeries with intraoperative TCeMEPs monitoring and DEX anesthesia agents, (2) studies that reported the effect of DEX on amplitude of TCeMEPs, (3) studies with only adult patients of age between 19 and 65 years old, (4) studies included patients with an American Society of Anesthesiologists physical status I, II, or III, (5) studies were published in English. Studies were excluded if they included patients with injury of nerve conduction pathways, diabetes, pregnancy, etc. The reference lists of studies were also screened.

Study Selection

Zotero, reference management software, was used to help manage the sources extracted from databases. After removing duplicates, we independently screened all titles and abstracts to exclude irrelevant studies that failed to meet the inclusion criteria. The final list of studies that met the inclusion criteria above is accepted to be relevant in investigating the effect of DEX on the amplitude of TCeMEPs.

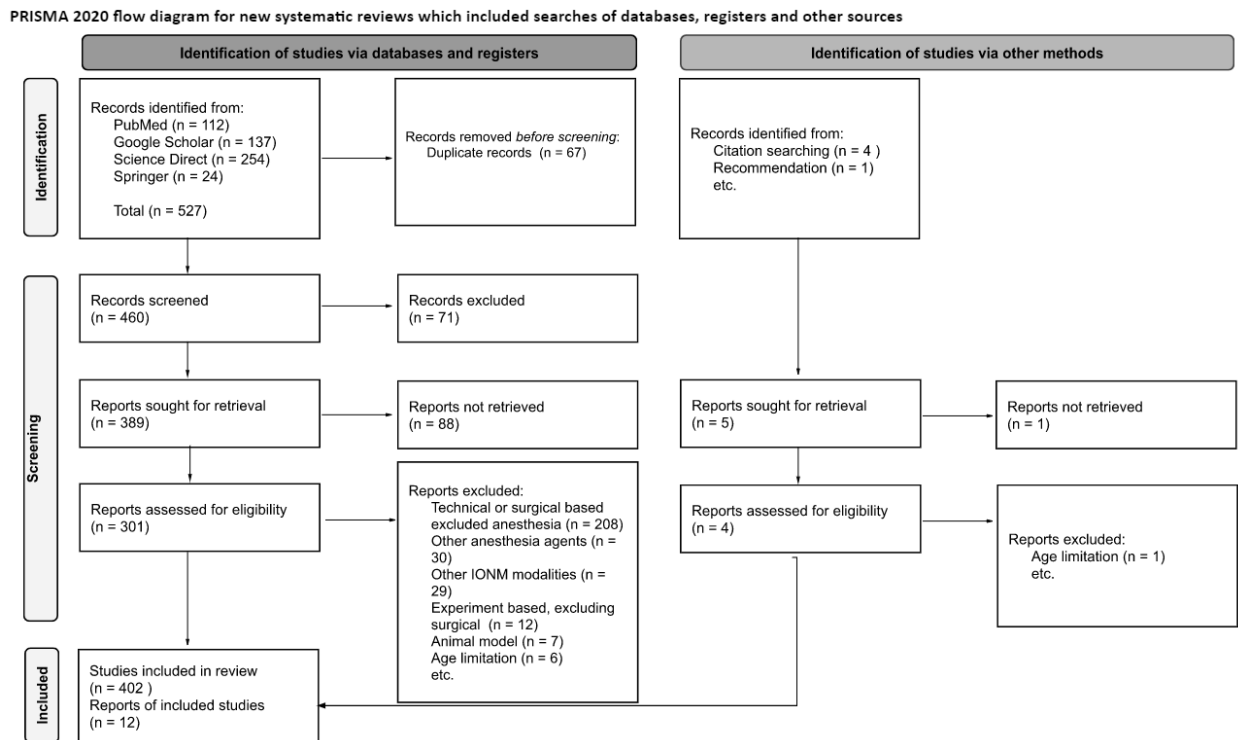


Figure 1. PRISMA flow diagram. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram illustrates the study selection flow.

Data Extraction

For each study selected, we screened and extracted data such as the dosage of DEX infusion, the presence of an initial bolus, TIVA regime, sample size, TCeMEPs amplitude at baseline and after DEX infusion, and the time when amplitudes were obtained. For the studies that did not report the amplitude of TCeMEPs,

the author recorded the number of incidents when TCeMEPs were lost during surgery instead and conducted another comparison group for evaluating the effect of different groups of DEX dosage on TCeMEPs amplitude.

Statistical analysis

The studies were grouped by the dosage of DEX used during operation (0.1-0.4 $\mu\text{g kg}^{-1} \text{h}^{-1}$, 0.5 $\mu\text{g kg}^{-1} \text{h}^{-1}$, 0.6 $\mu\text{g kg}^{-1} \text{h}^{-1}$, 0.8 $\mu\text{g kg}^{-1} \text{h}^{-1}$). Analysis was conducted using a univariate model to compare the baseline amplitude of different dosage groups and the amplitude after the infusion of DEX. Forest plots with random effects and 95% confidence were constructed. Cochran's Q test and I^2 statistics were also calculated to describe the percentage of variation across studies due to heterogeneity rather than chance (Higgins et al., 2019). A subgroup analysis can be one approach to explain heterogeneity (Higgins et al., 2019). Q values show the presence of heterogeneity, and I^2 values greater than 75% were interpreted as considerable heterogeneity. In addition, a secondary analysis was also conducted in the 0.5 $\mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion group to compare the effect of DEX loading dose. A tertiary analysis was performed to evaluate whether the combination of propofol-fentanyl interacting with DEX infusion can lead to an impact on the TCeMEPs amplitude in comparison to propofol-remifentanyl.

All the statistical analyses were performed using the SPSS software version 29.0. A *P* value of 0.10 was used to determine statistical significance (Higgins et al., 2019).

RESULTS

Literature search

Five hundred and twenty-seven papers were identified from the database search. In the prescreening process, 67 papers were found to be duplicated and removed. After screening titles and abstracts, 389 papers remained for full-text screening. After further screening for studies against inclusion criteria, 12 papers remained, with 402 participants included in this systematic review (Table 1). The process of study selection is shown in Fig 1.

Intraoperative data such as the dosage of DEX used the presence of DEX loading dose, the baseline amplitude of TCeMEPs, the amplitude after the induction of Dex, the time when amplitudes obtained after DEX infused (Table 2), and the number of TCeMEPs lost were collected for analysis (Table 3). The alarm criteria were defined as a greater than 50% decrease in the TCeMEPs amplitude (Legatt et al., 2016).

Study Characteristics

The 12 studies included 402 patients (Table 1). There were 9 studies with 317 patients that reported the amplitude value during certain times following the infusion of DEX. Among these nine studies (Table 2), 15.77% (50/317) of the patients were in the 0.1-0.4 $\mu\text{g kg}^{-1} \text{h}^{-1}$ DEX dosage group, 66.25% (210/317) of the patients in the 0.5 $\mu\text{g kg}^{-1} \text{h}^{-1}$ DEX dosage group, and 17.98% (57/317) of the patients were in the 0.6 $\mu\text{g kg}^{-1} \text{h}^{-1}$ DEX dosage group. Among the 0.5 $\mu\text{g kg}^{-1} \text{h}^{-1}$ DEX dosage group, 36.19% (76/210) of the patients had a DEX loading dose for over 10 minutes before the constant DEX infusion, and 28.57% (60/210) of the patients had anesthesia maintenance using propofol and fentanyl infusion.

Table 1: Patients' Demographics in the included studies (mean \pm standard deviation).

Study, Year	Sample size	Mean age	% Male	DEX dosage	Loading dose
Andleeb et al., 2021	30	42.73 \pm 14.86	70%	0.5	N
Bala et al., 2008	30	45 \pm 14	46.67%	0.3	N
Bala et al., 2008	30	45 \pm 14	46.67%	0.6	N
Chen, 2015*	14	71 \pm 6	57.14%	0.3	Y (0.3)
Chen, 2015*	14	67 \pm 5	64.28%	0.8	Y (0.8)
Lam et al., 2019 ^a	20	\geq 18	-	0.1-0.4	N
Lee, 2019*	40	54.0 \pm 16.5	55.00%	0.5	Y (0.5)
Li et al., 2015	23	41 \pm 13	56.52%	0.5	Y (0.5)
Lin, 2014*	17	58 \pm 12	47.06%	0.5	Y (0.5)
Liu et al., 2022	54	43.4 \pm 15.3	53.70%	0.5	N
Liu et al., 2022	53	42.9 \pm 15.7	58.49%	0.5	Y (1.0)
Mishra et al., 2020	9	26 \pm 15	55.60%	0.6	N
Pacreu et al., 2021	10	58.3 \pm 16.4	60%	0.5	N
Pacreu et al., 2021	10	48.10 \pm 16.92	60%	0.5	N
Rozet et al., 2015	18	54 \pm 3	25%	0.6	Y (0.6)
Sachdev et al., 2019	30	40.6 \pm 13.5	50%	0.5	N

DEX dosage, dexmedetomidine dosage ($\mu\text{g kg}^{-1} \text{h}^{-1}$).

*Studies included with no amplitude data reported.

^aStudies did not include mean age or gender.

Table 2. Intraoperative details for included studies (mean \pm standard deviation).

Study, Year	DEX dosage	Loading dose	Opioids	Baseline Amp.	Monitored Amp.	Time ^a
Andleeb et al., 2021	0.5	N	F	408 \pm 235	567 \pm 252.5	30
Bala et al., 2008	0.3	N	R	11.9 \pm 1.9	11.7 \pm 2.0	10-20
Bala et al., 2008	0.6	N	R	11.9 \pm 1.9	11.4 \pm 2.2	10-20
Lam et al., 2019	0.1-0.4	N	-	4.6 \pm 1.5	4.5 \pm 1.709	60-90
Li et al., 2015	0.5	Y (0.5)	R	354 \pm 161	292 \pm 163	30
Liu et al., 2022	0.5	N	R	1.0 \pm 0	0.913 \pm 0.065	20
Liu et al., 2022	0.5	Y (1.0)	R	1.0 \pm 0	0.774 \pm 0.0924	20
Mishra et al., 2020	0.6	N	F	2014 \pm 1298	869 \pm 1314	30
Pacreu et al., 2021	0.5	N	R	2092.56 \pm 1267.31	1975.78 \pm 1762.58	45
Pacreu et al., 2021	0.5	N	R	2254.19 \pm 1274.17	2153.02 \pm 1373.14	45
Rozet et al., 2015	0.6	Y (0.6)	R	65.1 \pm 194.8 ^b	-116.7 \pm 136.3	150 \pm 30
Sachdev et al., 2019	0.5	N	F	1199.1 \pm 1154.6	1226 \pm 1257	30

DEX dosage, dexmedetomidine dosage ($\mu\text{g kg}^{-1} \text{h}^{-1}$); Amp., amplitude; F, fentanyl; R, remifentanyl.

^aTime (minutes) when amplitudes were obtained after infusion of dexmedetomidine.

^bRozet et al. did not report baseline amplitude; thus, amplitude recorded at 60 \pm 30 mins following dexmedetomidine infusion was used to compare amplitude monitored at 150 \pm 30 mins after infusion.

On the other hand, there were three studies with 85 patients who did not have the amplitude value reported (Table 3). Among these three studies, 16.47% (14/85) of the patients were in the 0.1-0.4 $\mu\text{g kg}^{-1} \text{h}^{-1}$ DEX

dosage group, 67.06% (57/85) of the patients were in the 0.5 $\mu\text{g kg}^{-1} \text{h}^{-1}$ DEX dosage group, and 16.47% (14/85) of the patients were in the 0.8 $\mu\text{g kg}^{-1} \text{h}^{-1}$ DEX dosage group. All the patients in these three studies had the DEX loading dose for over 10 minutes before the constant DEX infusion, and 52.94% (45/85) of the patients had anesthesia maintenance using fentanyl opioids for analgesia.

Table 3. Intraoperative details for included studies with no amplitude data reported.

Study, Year	DEX dosage	Loading dose	Opioids	Baseline	Loading dose-positive case	Continuous infusion positive case
Chen et al., 2015	0.3	Y (0.3)	F	O	0 ^a	0 ^a
Chen et al., 2015	0.8	Y (0.8)	F	O	3 ^a	4 ^a
Lee et al., 2019	0.5	Y (0.5)	R	O	-	9 ^b
Lin et al., 2014	0.5	Y (0.5)	F ^d	O	-	0 ^c

DEX dosage, dexmedetomidine dosage ($\mu\text{g kg}^{-1} \text{h}^{-1}$); F, fentanyl; R, remifentanyl.

A positive case was defined as transcranial motor-evoked potential amplitude loss at any of the six muscles.

^bA positive case was defined as the amplitude's sudden reduction (>50%).

^cA positive case was defined as a reduction (>75%) of the amplitude at 60 minutes following dexmedetomidine infusion.

^dtomidate was used instead of propofol with a combination of fentanyl.

Data analysis

Studies with amplitude values were reported.

A total of 9 studies with 317 total patients have amplitude values reported with covariates, such as the presence of loading dose and the use of fentanyl as opioids. Using a random-effects model, the overall effect size was measured by Cohen's *d*, with $d = -0.32$, $p < 0.10$, indicating a significant small effect of 0.1-0.4 $\mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion on TCeMEPs amplitude with substantial heterogeneity ($\tau^2 = .17$, $I^2 = 0.68$) (Fig. 2).

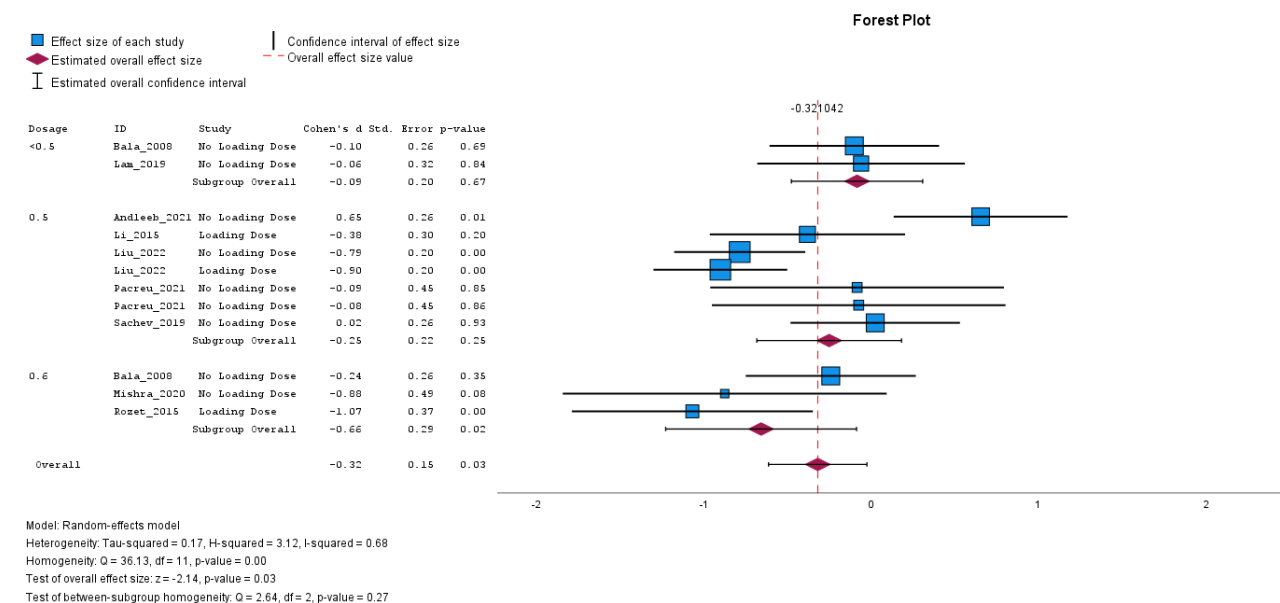


Figure 2. Forest plot of included studies with amplitude value reported.

Studies with amplitude values were reported by holding the TIVA regime and the absence of loading dose constant.

A total of 4 studies with 154 patients were included in this category. They were the studies that had the amplitude values reported, no fentanyl used for analgesia, and no DEX loading dose injected before the constant infusion of DEX. Using a random-effects model, the overall effect size was measured by Cohen's *d*, with $d = -0.30$, $p < 0.10$, indicating a significant small effect of $0.1\text{-}0.6 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion on TCeMEPs amplitude with minimal heterogeneity ($\tau^2 = .05$, $I^2 = 0.39$) (Fig. 3). Liu et al. (2022), consisting of the largest sample size of 54 patients, has the most significant weight with 25.62% in outcomes of intraocular pressure (IOP) result.

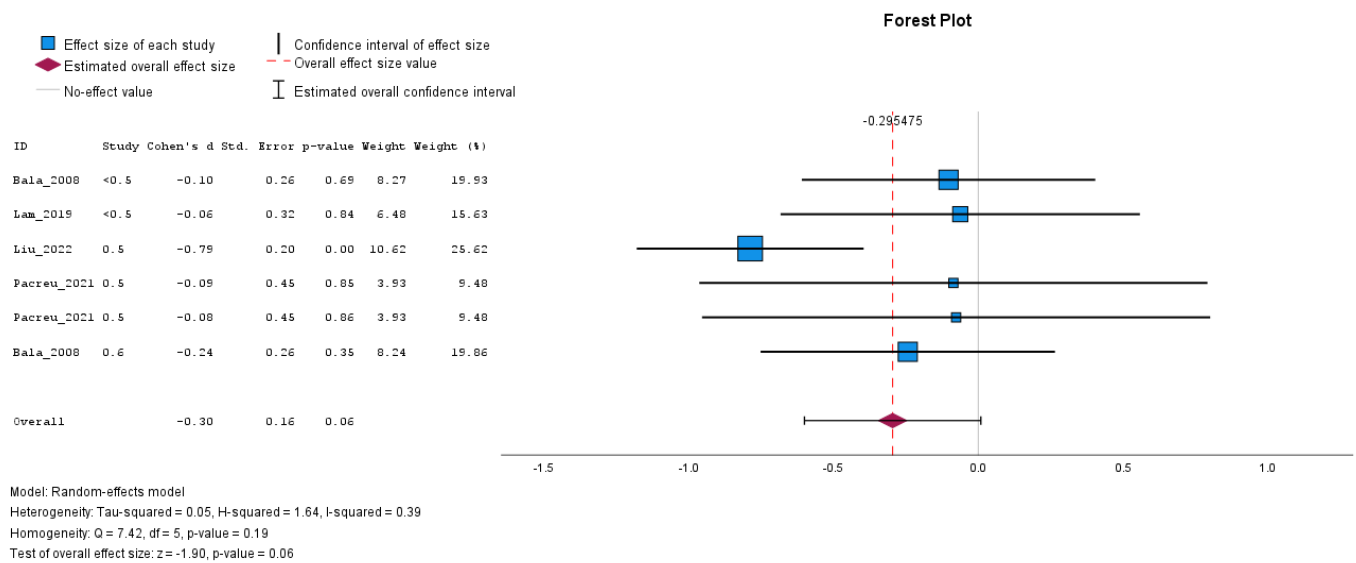


Figure 3. Forest plots included studies with reported amplitude values, propofol-remifentanyl regimes, and without dexmedetomidine loading doses.

Effect of loading dose interacting with $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion on TCeMEPs amplitude by holding TIVA regime constant

A total of 3 studies with 150 patients were included to evaluate the effect of DEX loading dose on the TCeMEPs' amplitude. This category only included studies with $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion and propofol-remifentanyl use for the TIVA regime. Li et al. (2015) had a loading dose of $0.5 \mu\text{g/kg}$ over 10 minutes, and Liu et al. (2022) had a loading dose of $1.0 \mu\text{g/kg}$ over 10 minutes before the constant infusion of $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX. Using a random-effects model, the subgroup overall effect size for the loading dose group was measured by Cohen's *d*, with $d = -0.69$, $p = 0.01$ (Fig. 4), indicating a significant medium effect of DEX

loading dose on TCeMEPs amplitude. This illustrated the depression of TCeMEPs amplitude when there was an injection of DEX loading dose over 10 minutes before the infusion of $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX. Lastly, according to the forest plot, there was minimal overall heterogeneity ($\tau^2 = .05$, $I^2 = 0.39$) between the loading and no loading dose groups.

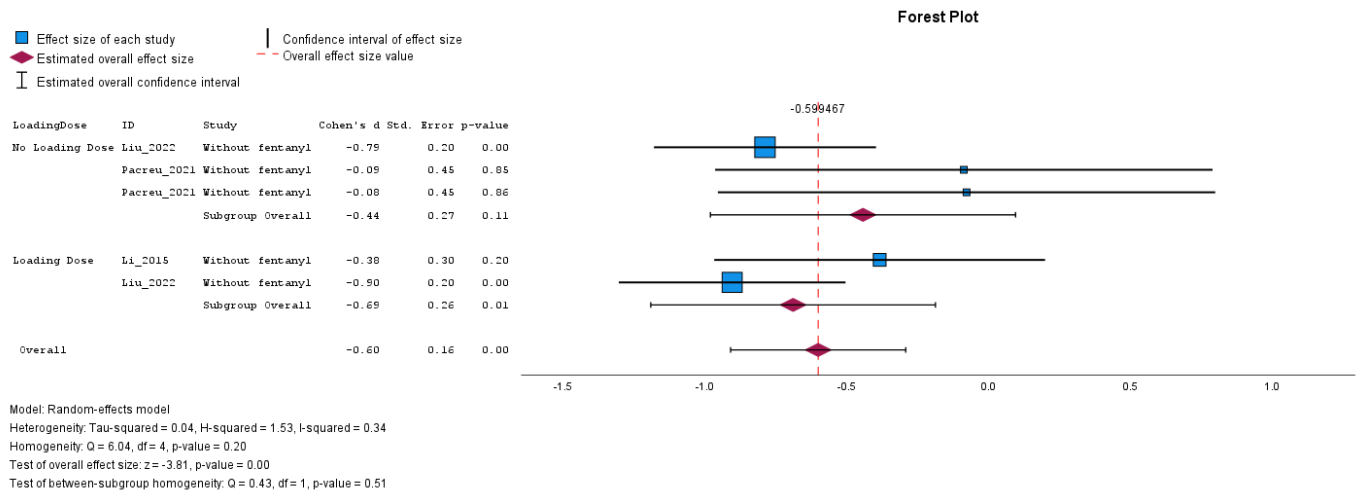


Figure 4. Forest plot included studies with amplitude values reported $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion and propofol-remifentanyl regime. The subgroups are the studies with or without dexmedetomidine loading dose.

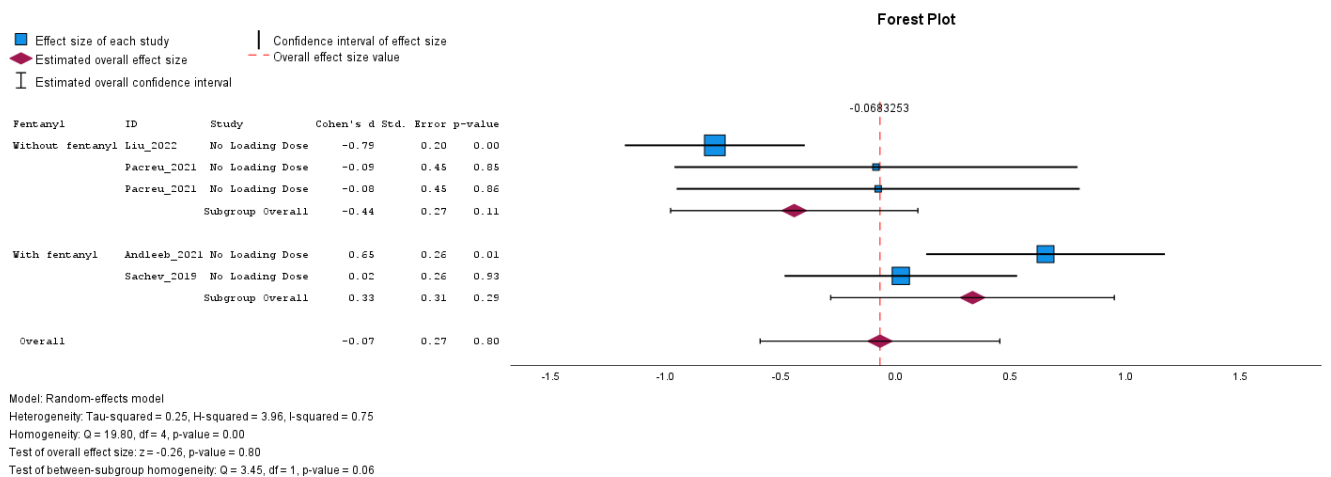


Figure 4. Forest plot included studies with reported amplitude values, $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion, and no dexmedetomidine loading group. The subgroups are the studies with or without the use of fentanyl for analgesia.

Effect of fentanyl interacting with $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion on TCeMEPs amplitude by the absence of loading dose constant

A total of 4 studies with 134 total patients were included in this category to evaluate the effect of fentanyl instead of remifentanyl on the TCeMEPs amplitude. This category only included studies with $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$

DEX infusion and without the use of loading dose. According to the random-effects model, the subgroup over-effect size for the fentanyl group was measured by Cohen's *d*, with $d = 0.33$, $p = 0.29$ (Fig. 5), indicating a non-significant small effect of fentanyl on TCeMEPs amplitude. However, there was an overall high heterogeneity ($\tau^2 = .25$, $I^2 = 0.75$) between the subgroups of patients with propofol-fentanyl and propofol-remifentanyl regimes.

Studies with amplitude values were reported.

Of the 85 total patients, 16.47% of the patients were in the $0.1\text{-}0.4 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX dosage group, 67.06% of the patients were in the $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX dosage group, and 16.47% of the patients were in the $0.8 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX dosage group. Given the clinically diverse studies on defining a positive case, a meta-analysis was not conducted (Higgins et al., 2019).

When comparing the two DEX dosage groups ($0.3 \mu\text{g kg}^{-1} \text{h}^{-1}$ and $0.8 \mu\text{g kg}^{-1} \text{h}^{-1}$) in Chen et al. (2015), although both groups have fentanyl used for analgesia and loading dose, the patients with $0.8 \mu\text{g kg}^{-1} \text{h}^{-1}$ had a significant difference in the incidence of TCeMEPs amplitude loss. The possible cause for the loss of amplitude may be the higher dose of DEX infusion with a higher bolus of DEX loading dose.

When comparing the patients in Lee et al. (2019) and Lin et al. (2014), although both groups have the exact DEX infusion dosage and the same amount of DEX loading dose, the patients with fentanyl used for analgesia had a noticeable reduction in the number of positive cases. However, given the difference in the definition of positive cases, the lesser amounts of positive cases in Lin et al. (2014) may be because this study collected the positive cases only at 60 minutes following DEX infusion, in comparison with Lee et al. (2014), which recorded the total amount of incidence throughout the surgery.

Table 3. Intraoperative details for included studies with no amplitude data reported.

Study, Year	DEX dosage	Loading dose	Opioids	Baseline	Loading dose-positive case	Continuous infusion positive case
<i>Chen et al., 2015</i>	0.3	Y (0.3)	F	0	0 ^a	0 ^a
<i>Chen et al., 2015</i>	0.8	Y (0.8)	F	0	3 ^a	4 ^a
<i>Lee et al., 2019</i>	0.5	Y (0.5)	R	0	-	9 ^b
<i>Lin et al., 2014</i>	0.5	Y (0.5)	F ^d	0	-	0 ^c

DEX dosage, dexmedetomidine dosage ($\mu\text{g kg}^{-1} \text{h}^{-1}$); F, fentanyl; R, remifentanyl.

A positive case was defined as transcranial motor-evoked potential amplitude loss at any of the six muscles.

^bA positive case was defined as the amplitude's sudden reduction (>50%).

^cA positive case was defined as a reduction (>75%) of the amplitude at 60 minutes following dexmedetomidine infusion.

^dEtomidate was used instead of propofol with a combination of fentanyl.

DISCUSSION

Intraoperative MEP monitoring is found to have a high sensitivity and specificity to predict neurological injury (Lin et al., 2014). TIVA with propofol is commonly used for surgeries that undergo TCeMEP

monitoring (Legatt et al., 2016). However, the prolonged or considerable dosage of propofol used may lead to propofol-related infusion syndrome (PRIS), such as hypotension, metabolic acidosis, renal failure, and rhabdomyolysis (Annecke et al., 2012).

DEX, an α^2 -receptor agonist, has been commonly used as a TIVA adjuvant to provide analgesia and sedation with negligible respiratory depression and a promise of hemodynamic stability (Bala et al., 2008; Li et al., 2015). The adjunct of DEX can help reduce intraoperative consumption of the TIVA regime, and the α^{2A} -receptor subtypes in DEX may protect against hypoxic and excitotoxic injuries (Bala et al., 2008). Previous studies investigated the effect of DEX on MEP. The results are controversial due to the covariances, such as different sample groups, different DEX dosages used, the presence of DEX bolus, and the other opioids used (Mahmoud et al. (2007); Mahmoud et al. (2010); Bala et al. (2008); Liu et al. (2022)). No meta-analysis was found discussing the effect of different dosages of DEX infusion on TCeMEP amplitude in adult populations. Given the possibility of MEP changes, including irreversible changes, and losing TCeMEPs signal that can lead to postoperative neurological deficits, it is critical to consider different variances that can interact with DEX infusion and cause susceptibility of TCeMEPs monitoring.

The results of this systematic review and meta-analysis demonstrate that the $0.1\text{-}0.6 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion has a significant mild depression on TCeMEPs amplitude with minimal heterogeneity by holding the TIVA regime and the absence of DEX bolus constant (Fig. 3). This result is consistent with Bala et al. (2008). Compared to alarm criteria (50%), the effect size is so tiny that indicates a DEX infusion – up to $0.6 \mu\text{g kg}^{-1} \text{h}^{-1}$ – is appropriate to be considered as a TIVA adjunct. The results also show that the presence of a DEX loading dose before a constant $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion significantly causes a medium effect of depression on TCeMEPs amplitude (Fig. 4). However, due to the limited number of studies in the subgroups with and without DEX bolus, we can only provide a moderate heterogeneity result between subgroups.

The effect of constant $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion on TCeMEPs amplitude also seems to vary between subgroups of patients with or without the combination of fentanyl for analgesia (Fig. 5). The high heterogeneity between subgroups indicates the use of propofol-fentanyl instead of propofol-remifentanyl causes an increase in MEP amplitude even when there is a constant $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion. However, the results were insignificant given the limited number of included studies.

When analyzing individual studies with no amplitude data, they reported a higher incidence rate in the higher DEX dosage group ($0.8 \mu\text{g kg}^{-1} \text{h}^{-1}$) with a higher amount of bolus, which is consistent with our results in a meta-analysis. The lower incidence rate in the patient group with the use of fentanyl opioids interacting with DEX infusion also supports our findings. The use of fentanyl for analgesia may reduce the susceptibility of DEX infusion.

Taken in aggregate, the constant infusion of DEX – up to $0.6 \mu\text{g kg}^{-1} \text{h}^{-1}$ – is appropriate to be considered as a TIVA adjunct in the adult population when interacting with propofol-remifentanyl and with no initial bolus of DEX given. The use of propofol-fentanyl may reduce the suppression of DEX infusion on TCeMEPs

amplitude. However, previous studies found remifentanyl is associated with more profound analgesia intra-operatively and lower post-operative pain scores in comparison with fentanyl. It is critical to consider the possibility of obscuring TCeMEPs amplitude when using higher doses of DEX or when the initial bolus of DEX is given before constant infusion of DEX as an adjunct.

Limitations

Certain limitations should be acknowledged when interpreting the findings from this review. First, although the effect of $0.1-0.6 \mu\text{g kg}^{-1} \text{h}^{-1}$ DEX infusion seems to have only a mild depression on TCeMEPs amplitude, we cannot reject the possibility it may attenuate the signal by an amount more significant than the alarm criteria. Previous studies have found a controversial result of false favorable rates (changes in TCeMEPs without post-operative neurological deficits), which may or may not increase with DEX infusion (Hyung Lee et al., 2019; Pacreu et al., 2021). Further studies are needed to investigate the effect of DEX infusion on false-positive rates by taking the covariances into account, such as initial bolus, the opioids used, etc. Second, many studies included in this review were conducted where amplitude data was obtained in specific timeframes with a significant time interval (e.g., T1 as baseline before the infusion of DEX and T2 as 30 minutes after DEX infusion. The big-time gap between data collection may lead to a failure to capture significant signal loss; for example, Mahmoud et al. (2007) found a significant decrease in amplitude at approximately 10 minutes after the initial bolus injection. Therefore, we cannot reject the possibility that DEX infusion may attenuate the TCeMEPs amplitude outside of recorded time. This could have led to a variation, even though the results show zero positive cases at 60 minutes following DEX administration (Lin et al., 2014). Future studies should include a better experiment design to improve this limitation. Third, our study excluded the pediatric and elderly (>80) populations because these population groups may be more sensitive to anesthesia dosage. Further studies are needed to investigate the effect of DEX infusion on TCeMEP amplitude in pediatric and elderly populations. Lastly, the major limitation of our study is the small sample size, which could have led to potential bias in our conclusion. Future studies should be conducted to retest the reliability of the results found in this review.

CONCLUSION

Our study found that a DEX infusion of $0.1-0.6 \mu\text{g kg}^{-1} \text{h}^{-1}$ without an initial bolus only slightly suppresses TCeMEPs amplitude. Therefore, a low DEX dosage can be considered an appropriate TIVA adjunct for adults. However, certain covariances, such as initial loading dose and fentanyl, may cause variations in monitored amplitudes when interacting with this low-dosage DEX infusion.

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