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Dexmedetomidine versus Midazolam as Premedication in Anesthesia: A Meta-Analysis from Randomized Controlled Clinical Trials

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Abstract

Dexmedetomidine [Dex] is an α2-adrenoceptor agonist which provides sedation, analgesia and anxiolytic effects, thus making it a potentially useful anesthetic premedication. A number of clinical trials have been conducted to compare the sedative effect of Dex versus midazolam [Mdz], a conventional sedative agent in anesthesia. Nevertheless, consensus has not been achieved on which agent is superior to the other in terms of the overall benefit to patients. In this study, we have isolated four independent studies containing randomized, controlled, clinical trials on patients and compare the efficacy and safety of these two agents as a premedication in anesthesia. In the studies of the catheter ablation of atrial fibrillation and surgical correction of scoliosis deformities, Dex treatment resulted in a better sedative and analgesic effects, reflected by a reduced pain, a lower dose of analgesic agents required, and greater sedation scores than Mdz treatment. Similarly, intranasal Dex premedication in the children's dental rehabilitation and adenotonsillectomy, Dex also yielded a better efficacy. Taken together, Dex provides an improved premedication for sedation and analgesia, as well as the protective effects on the end organs. This study has provided evidence for optimized sedation protocol in anesthesia.

Keywords: Dexmedetomidine; Midazolam; Anesthesia; Clinical trials

Introduction

Premedical sedation and analgesia greatly facilitate surgical procedures and secures the success of a surgery to cure human diseases. This premedication of sedation and anesthesia can reduce the pain, anxiety or agitation through introducing the sedative medicines into the human body. Most of the sedative and analgesic drugs target the nervous system. One of them, Midazolam [Mdz], is a very versatile drug widely used in general anesthesia [1-4]. It can be administered into the body intramuscularly [5-7], intravenously [8,9], or orally [10,11]. Mdz is an inhibitor of gamma-amino-butyric acid [GABA] receptor with a rapid action, usually 2-3 minutes intravenous administration and 15 minutes by intramuscular, oral, nasal administration [12-15]. It can be rapidly absorbed in human tissues and acts on the nervous system [16]. Midazolam was approved by FDA in 1986 and used as a conventional premedication in outpatient endoscopy and dentistry [17-19]. Since Mdz doesn't have the analgesic function, additional medicines, such as opioid, are often used in combination with Mdz.

Recently, dexmedetomidine [Dex], a highly selective α2 adrenoceptor agonist, has been discovered to have a potent effect on sedation and analgesia without respiratory depression [20-24]. It provides a unique "conscious sedation", a state of staying awake with a reduced pain [25]. The Dex-α2 receptor interaction gives rise to a negative feedback on the release of the neurotransmitter, norepinephrine. This inhibition subsequently leads to anesthesia [24]. Dexmedetomidine has been approved by US FDA in 1999, and has often been used for surgical, endoscopic and imaging procedures [26].

An increasing number of studies have been performed to test the clinical effects of Mex and compare the efficacy and safety between Dex and Mdz premedication [27-31]. It is very important to validate these clinical investigations and provide a comprehensive understanding of the effects of these medicines on sedation and analgesia. In this study, we analyzed four randomized, independent clinical studies using meta-analysis and concluded Dex as an effective premedication for sedation and analgesia.

Methods

Database and search strategy

We searched the following database for relevant studies: PubMed (from 2000 to February 2014) and EMBASE (from 2000 to February 2014). Search terms used for PubMed are: "dexmedetomidine" [All Fields] AND "midazolam" [All Fields] AND ("anesthesia" [All Fields] OR "anaesthesia" [All Fields] AND (Clinical Trial([ptyp] AND ("2000/01/01" [PDAT]: "2014/4/28"[PDAT])). Search terms used for EMBASE are: 'dexmedetomidine' and 'midazolam' and ('anesthesia'/exp or 'anaesthesia'/exp and [controlled clinical trial]/lim and [2000-2014]/py.

Selection criteria

Eligible studies are selected based on following criteria: 1) study design: randomized controlled clinical trials (RCTs); 2) subjects: Adult and pediatric patients who underwent surgery; 3) intervention: dexmedetomidine vs midazolam. Two authors (Chuixian Zhou and Junhui Zhao) independently conducted the study selection based on these criteria. Any discrepancy was resolved by group discussion by both authors.

Quality assessment

The quality of included trials was assessed using the Jadad scale score (0 to 5), with a score of 3 or above indicating high quality [32].

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Outcome

Primary outcomes for the assessment of Dex efficacy are: pain scores, consumption of the analgesic drugs (remifentanil or fentanyl), and satisfactory level with mask application.

Data extraction and statistical analysis

Following information were extracted from selected studies: author, publication year, trial phase, number of patients enrolled, treatment regimen, median age, sex percentage, pain scores, consumption of the analgestic drugs (remifentanil or fentanyl), and satisfactory levels with mask application. Mean difference and the associated 95% confidence interval (CI) for pain scores and consumption of the analgestic drugs (remifentanil or fentanyl), and risk ratio and the associated 95% CI for satisfactory with mask application, were used to assess treatment efficacy. The χ^2 Cochran Q test was used to detect heterogeneity (variability in the intervention effects) across different studies. Random or fixed-effects inverse variance weighted method was employed for the pooled efficacy analysis depending on the result of heterogeneity test [33]. All analyses were performed using the Review Manager, version 5.1.0 (Cochrane Collaboration, Oxford, UK).

Results

Improved sedation and analgesia in adults or adolescent patients

Through PubMed and EMBASE search detailed as in Methods above, we have selected four independent clinical studies from different research groups, briefly summarized in Table 1. Dex and Mdz premedications were compared in these studies for patients who were subjected to the various surgery procedures. Cho et al. studied Dex for the anesthesia in the patients undergoing atrial fibrillation [A-fib] surgery [34]. Ninety adult patients were randomly chosen for this study. In the A-fib surgery, deep sedation and analgesia are crucial since the catheter ablation of A-fib is a long procedure, about 2-4 hours and discomfort from the patient may become a risk factor for the success of the surgery. Cho et al. compared the effects of either Dex or Mdz with remifentanil, a selective mu opioid receptor agonist with a rapid effect [35,36]. It gave twice as potent action as fentanyl which was used in Aydogan's research study described as below. Cho et al. investigated the sedation levels [measured via the Ramsay sedation and bispectral index score], haemodynamic variables, pain score (10-point numeric scale), satisfaction levels of the patients and cardiologists.

Similarly, Aydogan et al. compared both Dex and Mdz's effect in the sedation during a pediatric surgery, scoliosis [37]. 42 juvenile adults (aged 12-18 years old) patients with scoliosis were randomly distributed for treatment in the study. The surgery of scoliosis correction contains lots of pain and early postoperative pain control is very crucial for the patient care. The efficacy of the sedation was measured by the Richmond Agitation Sedation Scale [RASS]. Pain relief was assessed by the Numeric Visual Analog Scale [NVAS]. Also, intermittent fentanyl was used to combine with DEX or MDZ administration. Similar to remifentanil, fentanyl is a potent and synthetic analgesic drug, a strong agonist at the μ-opioid receptors [38,39].

Both Cho and Aydogan's studies are very similar in terms of patient subjects, premedication method, and the evaluation outcomes. Besides, the dosages of Dex and Mdz used were very close; 0.2-0.7 μg/kg/h Dex was used by Cho et al., compared to 0.4-0.5 μg/kg Dex in Aydogan's study. Mdz used by Cho group was 0.14-0.2 mg/kg, a similar dose to 0.15-0.2 mg/kg by Aydogan. Importantly, both studies demonstrated the same results of the improved sedation with Dex over Mdz.

Since only figure data was available from Cho's study about the sedation levels, comparison can't be made (Figure 1). Instead, we analyzed a common outcome, the pain score by using meta-analysis. Figure 2 shows that Dex premedication gave rise to a reduced pain scores than Mdz treatment (Figure 2A). Correspondingly, the satisfactory levels from the cardiologist or the patients were increased with the Dex treatment. In addition, the required dose of another

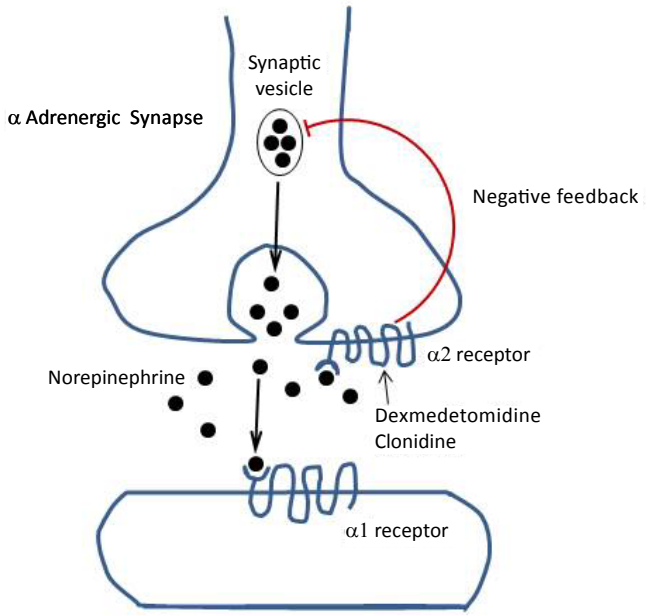

Figure 1: Action of dexmedetomidine on the neurotransmitter signaling in the synapse. Dex or Clonidine can work as an agonist for the alpha-2 adrenoceptor, an opioid receptor. This interaction had a negative effect on the release of the neurotransmitter which eventually results in the attenuation of neurotransduction, such as the pain relief. Modified from Dexmedetomidine.com and Gertler et al., [24].

Authors	Patients (age)	Surgery involved	Outcomes measured
Cho et al. [34]	90 adults (20-70)	Catheter ablation of atrial fibrillation	Ramsay sedation scores; Bispectral index scores; Haemodynamics; Pain scores; satisfaction levels
Aydogan et al. [37]	42 children (12-17)	scoliosis	Efficacy of sedation by RASS; Pain relief by NVAS; Delirium by Confusion Assessment Method; Fentanyl consumption; Hemodynamics
Sheta et al. [40]	82 children (3-6)	dental rehabilitation	4-point sedation scale; mask acceptance; hemodynamics
Akin et al. [41]	90 children (2-9)	adenotosillectomy	Observer Assessment of Alertness and Sedation Scale; satisfactory mask induction; hemodynamics; separation with parents.

Table 1: Summary of the studies used for meta-analysis.

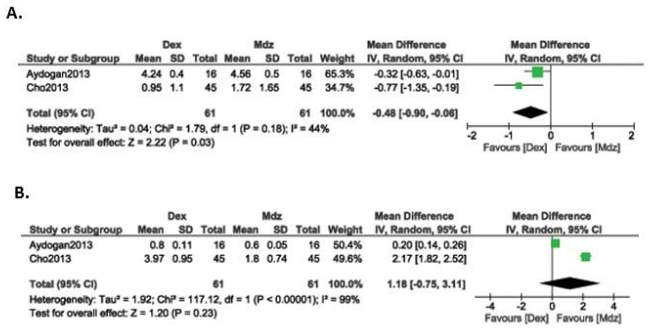

Figure 2: Dex premedication yields a lower pain score and less analgesic agent's requirement in the adult patients. Meta-analysis was performed to compare the pain scores and the consumption of the analgesic drugs (remifentanil or fentanyl) between Dex- and Mdz-premedicated adult patients. Rev5 analysis program was used in a random model.

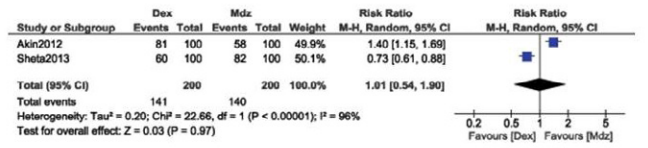

Figure 3: Satisfactory acceptance between Dex and Mdz premedication by the children patients.

Satisfactory compliance with mask application from Sheta's study and satisfactory mask induction from Akin's study were compared and data-analyzed with Rev5. There is no significant difference between Dex and Mdz intranasal medication.

sedation medicine, remifentanil or fentanyl was much lower in DR group (Figure 2B). Finally, delirium was used as a marker to assess the outcome of the sedation in Aydogan's study. Surprisingly, Dex gave rise to a lower effect of this symptom than Mdz did, indicating more beneficial effects of the Dex premedication.

Sedation effects on the children patients

Sedation in pediatric surgery is even more important than that in adults. Obviously, children may not co-operate with the doctors and are emotionally difficult to handle. Sheta's and Akin's group performed randomized clinical studies to compare the Dex and Mdz in sedation and analgesia. In both groups, the dosages and administering methods of Dex and Mdz were the same: intranasal 1 μg/kg Dex versus 0.2 mg/kg Mdz.

Sheta et al. compared Dex and Mdz premedications in children dental rehabilitation [40]. The patients were intranasally injected with Dex or Mdz. Seventy two children were recruited for the study. The patients' sedation status, mask acceptance, and hemodynamic parameters were recorded. Similarly, Akin et al. analyzed Dex and Mdz effect on the children with the elective adenotonsillectomy surgery [41]. The satisfactory mask induction and effect of both Dex and Mdz for 90 children aged from 2-9 years old who were measured as the outcomes for the action.

As for the sedation efficiency, Sheta group favors Dex and concluded a significant improvement of Dex while Akin's conclusion stays neutral; both medicines are equally efficient for sedation. Dex gave rise to a higher sedative scores than Mdz within 15 minutes [p=0.02] [40], further consolidating the better treatment of Dex. The meta-analysis of the satisfactory levels for their mask application for this premedication demonstrated that there was no significant difference between Dex and Mdz treatment (Figure 3). Also the sedation scores did not change so dramatically as those in adult patients from Cho and Aydogan's studies. This indicates a better method needed for the further to administer Dex into the children patients.

We also compared the effects of haemodynamics by MDZ and DEX treatment. Heart rates were measured in Aydogan2013 and Cho2013. DEX treated patients had a lower heart rate than MDZ treated ones: from 1 hr to 24 hrs in Aydogan2013, the heart rates in MDZ group were greatly increased than MDZ. Cho2013 also had the same tendency, although the difference failed to reach a statistical significance. In other studies, Sethi et al. [42], Arpaci and Bozkirli [43], Karaaslan et al. [44] also reported the similar conclusion from a different time points. Although it is difficult to perform a meta-analysis for these results,

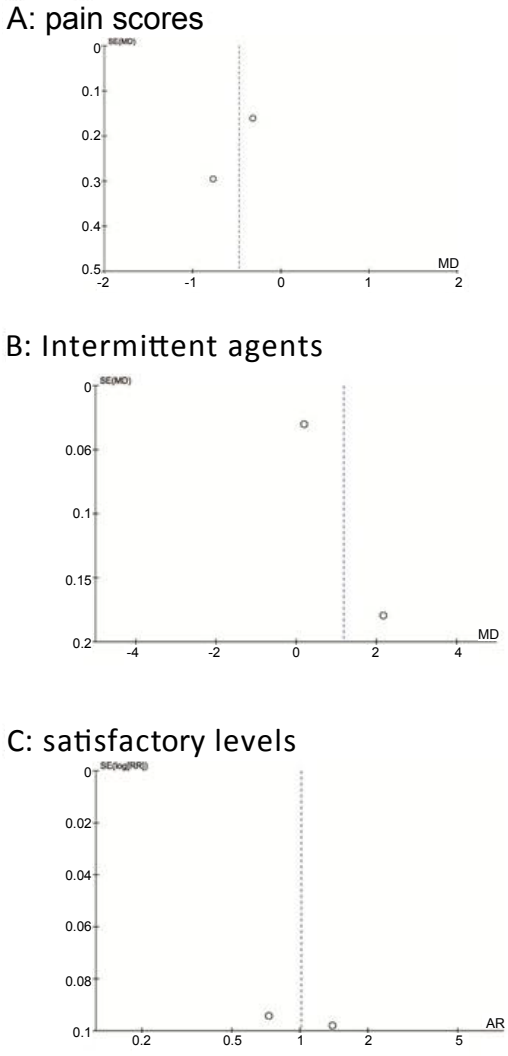

Figure 4: Funnel plots demonstrate the non-biased data results from the studies analyzed. Pane A includes the pain scores, panel B stands for the intermittent agent required from Aydogan 2013 and Cho 2013 studies, and panel C shows the satisfactory levels from Akin 2012 and Sheta 2013 studies. Symmetrical distribution of the data value suggests the non-bias of the studies chosen for analysis.

the effects of DEX over MDZ remained the same. Meanwhile, this effect was validated by another haemodynamic variable, mean arterial pressure [MAP]; in general, DEX treated patients had a reduced MAP values [34,37,42-44].

Adverse effects of Dex versus Mdz premedication

The side effects were evaluated in these studies, such as bradycardia, hypotension, desaturation, nausea. No difference was found between Dex and Mdz treatment. Also, no major difference in haemodynamics was noted in Cho and Aydogan studies, confirming the further use of this drug in the premedication.

Publication bias assessment

Begg's funnel plot was used for the assessment of the publication bias of selected studies used for meta-analysis [45]. The analyzed results for the pain scores, the intermittent agent required and satisfactory levels were individually plotted in Figure 4. The symmetrical patterns of these plots indicate no publication bias in selected studies.

Discussion

In this study, we have performed meta-analysis of four randomized clinical studies to compare the efficiency between Dex and Mdz for sedation and anesthesia. We concluded the improved efficacy of Dex over Mdz in premedication of sedation and analgesia. Among four studies analyzed here, two groups chosen the adults and two for the children as the subjects. In the adult patients, Dex was demonstrated to have more potent action than Mdz. However, this difference was not as dramatic as that in children from Akin's study. But the sedation scores were higher in Dex treated group than in Mdz-treated group at 10 minutes after drug administration [41]. Another group study using the children as the subject favored the Dex effect; Yuen et al. supported the improved action of Dex in the children's sedation and analgesia [29]. This discrepancy was attributed to the extra-long time of Akin's group, 45-60 minutes, compared to 40 minutes in Sheta's group [40].

Pain scores were measured in three of four studies using different measurements and the results are unanimously the same; Dex treatment gave a lower pain score than Mdz. Therefore, Dex has a general effect on the pain reduction in either adult or children patients.

Another α-2 adrenoceptor agonist, clonidine, has a long effect on anesthesia. Dex is chemically related to clonidine, about 8 times more specific for α-2 adrenoceptors. Therefore, Dex is more selective and potent medicine for sedation and analgesia [46]. In addition, Dex has a short half-life [2-3 hrs] while clonidine can last 12-24 hrs [47].

Lastly, Dex has been shown to have other beneficial effects, such as myocardial ischemia and cardioprotection [48-50], neuroprotection [51], and renoprotection [52,53]. These features enhance the potential of this premedication. Although Dex has been reported to have side-effects of bradycardia, hypotension, nausea, hypoxia [54-56], we did not find the significant difference between Dex and Mdz treatment.

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