Efficacy of perioperative dexmedetomidine in postoperative neurocognitive function: a meta-analysis

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SUMMARY

Neuroprotective effects of dexmedetomidine are reported in preclinical and clinical studies but evidence regarding the postoperative neurocognitive function is not as clear. This study performed a meta-analysis on outcomes of studies which examined neurocognitive performance by using valid assessment tools before and after perioperative dexmedetomidine treatment. Literature was searched in several electronic databases and studies were selected by following precise inclusion criteria. Meta-analyses of mean differences in percent changes from baseline in neurocognitive assessment scores were carried out and subgroup analyses were performed. Eighteen studies were included. Initial dose of dexmedetomidine (mean ± SD) was 1.28 ± 0.97 µg/kg and maintenance dose was 0.41 ± 0.11 µg/kg per hour. In healthy volunteers, there was no significant difference in the neurocognitive performance between dexmedetomidine and controls/comparators (mean difference (95% confidence interval (CI)): −12.72 (−50.25, 24.80) %; P = 0.51). Perioperative dexmedetomidine treatment was associated with significantly better neurocognitive performance in comparison with saline (mean difference (95% CI): 9.10 (3.03, 15.16) %; P = 0.003) as well as with comparator anaesthetics (mean difference: 5.50 (0.15, 10.86) %; P = 0.04) treated patients. In the sub-meta-analyses of studies which utilized neurocognitive assessment tools other than Mini-Mental State Examination (mean difference: 6.66 (−3.42, 16.74); P = 0.20) or studies with patients under 60 years of age (mean difference: 7.48 (−3.00, 17.96); P = 0.16), the differences were not significant between dexmedetomidine- and saline-comparator-treated patients. Perioperative dexmedetomidine treatment is associated with significantly better neurocognitive function postoperatively in comparison with both saline controls and comparator anaesthetics (predominantly midazolam).

Key words: Perioperative dexmedetomidine, postoperative cognitive dysfunction, postoperative neurocognitive dysfunction.

INTRODUCTION

Postoperative or post-anaesthesia neurocognitive dysfunction including emergence agitation, delirium and cognitive dysfunction have implications on the length of hospital stay and quality of care; children, elderly and cognitively fragile patients are at an increased risk. Delirium is a predictor of cognitive impairment in elderly patients without critical illness. This form of neurocognitive dysfunction can affect up to 80% of mechanically ventilated intensive care unit (ICU) patients. Emergence agitation can also be hazardous and may cause serious consequences for the patient such as injury, pain severity, and haemorrhage. In elderly patients, surgery, especially cardiac and orthopaedic, and general anaesthesia contribute in the development or promotion of cognitive dysfunction and dementia, and hence, the most important determinants of the postoperative cognitive function are the preoperative cognitive status and perioperative management.

Dexmedetomidine is a potent and highly selective transmembrane G protein coupled central γ2-receptor agonist which decreases central nervous system sympathetic outflow and provides sedation, analgesia, and anxiolysis besides reducing blood pressure and heart rate without respiratory depression. Sleep electroencephalographic studies have revealed that dexmedetomidine sedation resembles S2 sleep in humans. Moreover, opioid-sparing effects of dexmedetomidine are well known. These properties make it a suitable option for sedation in the ICU and in perioperative conditions.

Dexmedetomidine is reported to have considerable delirium preventing potential in ICU patients presumably because of its gamma-aminobutyric acid (GABA) receptor-sparing activity. Preclinical studies with animal models have indicated that dexmedetomidine provides neuroprotective effects and improve cognitive function after surgery. In clinical studies, however, whereas many have reported beneficial effects of dexmedetomidine in reducing neurocognitive side effects, others could not arrive at the similar conclusions. In order to gain refined evidence, the present study systematically reviews and meta-analyzes the outcomes of the relevant randomized controlled trials (RCTs) which utilized dexmedetomidine with general anaesthesia perioperatively or as ICU sedation and assessed baseline and...
postoperative/post-infusion neurocognitive function by using a reliable neurocognitive assessment tool.

RESULTS

Eighteen studies\textsuperscript{13–30} were finally selected for inclusion in the present meta-analysis. A flowchart of the study screening and selection process is given in Fig. 1. Major characteristics of the included studies relevant to the present study are presented in Table S1. Quality of the included studies was generally moderate to good. Selection biases including publication bias were also evident upon the visual examination of the funnel plot (Fig. S1).

From the included studies, data of 757 patients (age: 53.55 ± 7.28 years; weight 70.48 ± 12 kg and height 169.1 ± 6.6 cm) is used in the meta-analyses. In these studies, the initial dose of dexmedetomidine (mean ± SD) was 1.28 ± 0.97 µg/kg and maintenance dose was 0.41 ± 0.11 µg/kg per hour. Neurocognitive assessment was carried out with Mini-mental State Examination (MMSE) in 11 and Digital Symbol Substitution Test (DSST) in five studies. Emergence Agitation Score and Trail Making Test were used in one study each.

Main findings of the meta-analysis are summarized in Table 1. In young healthy volunteers, pooling of five datasets from three studies\textsuperscript{13–15} could not find any significant difference in the percent change from baseline (pre-infusion) in the performance of a neurocognitive assessment test between dexmedetomidine and control/comparator treatment (overall mean difference (95% confidence interval (CI)): −12.72 (−50.25, 24.80); \( P = 0.51 \); Random effects model; Fig. 2).

Perioperative dexmedetomidine treatment was associated with significantly better neurocognitive performance in comparison with saline- and comparator-treated patients collectively (mean difference (95% CI) in percent changes from baseline in neurocognitive scores: 7.84 (3.03, 12.65); \( P = 0.001 \); REM; Fig. 3). Distinctly, dexmedetomidine treatment was associated with significantly better performance in comparison with saline treated controls (mean difference: 9.10 (3.03, 15.16) %; \( P = 0.003 \)) as well as in comparison with comparator anaesthetics (mean difference: 5.50 (0.15, 10.86); \( P = 0.04 \); Fig. 3). When the effect sizes of dexmedetomidine vs controls and dexmedetomidine vs comparators meta-analyses were subjected to a Chi squared test, the difference was statistically non-significant (\( \chi^2 = 0.01; P = 0.94 \)).

In the subgroup analyses (Table 1), sub-meta-analysis of patients under 60 years of age led to non-significant difference between dexmedetomidine and comparator treated or control patients (mean difference: 7.48 (−3.00, 17.96); \( P = 0.16 \); \( P = 0.27 \); REM, as against patients over 60 years age: 8.34 (5.61, 11.07); \( P < 0.00001 \); REM; Fig. S2). Sub-meta-analysis of

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**Table 1** Summary of the meta-analyses outcomes

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Studies</th>
<th>Patients</th>
<th>Fixed effect</th>
<th>Random effects</th>
<th>( I^2 (%) )</th>
<th>( I^2 ) after sensitivity analyses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>17</td>
<td>757</td>
<td>11.14 (10.47, 11.82); ( P &lt; 0.00001 )</td>
<td>7.84 (3.03, 12.65); ( P = 0.001 )</td>
<td>98</td>
<td>79</td>
</tr>
<tr>
<td>DEX vs control (saline)</td>
<td>11</td>
<td>536</td>
<td>11.68 (10.98, 12.39); ( P &lt; 0.00001 )</td>
<td>9.10 (3.03, 15.16); ( P = 0.003 )</td>
<td>98</td>
<td>78</td>
</tr>
<tr>
<td>DEX vs comparators</td>
<td>6</td>
<td>221</td>
<td>6.15 (4.00, 8.30); ( P &lt; 0.00001 )</td>
<td>5.50 (0.15, 10.86); ( P = 0.04 )</td>
<td>90</td>
<td>77</td>
</tr>
<tr>
<td>Healthy individuals</td>
<td>3</td>
<td>74</td>
<td>−11.75 (−23.15, −0.35); ( P = 0.04 )</td>
<td>−12.72 (−50.25, 24.80); ( P = 0.51 )</td>
<td>91</td>
<td>87</td>
</tr>
</tbody>
</table>

**Subgroup analyses**

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Studies with</th>
<th>Studies/patients</th>
<th>Mean difference (95% CI) between DEX treated and control subjects</th>
<th>Subgroup differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 Age over 60</td>
<td>8 (385)</td>
<td>8.34 (5.61, 11.07); ( P &lt; 0.00001 ); REM; ( I^2 = 85% )</td>
<td>( \chi^2 = 0.02; P = 0.88; I^2 = 0% )</td>
<td></td>
</tr>
<tr>
<td>A2 Age under 60</td>
<td>9 (392)</td>
<td>7.48 (−3.00, 17.96); ( P = 0.16 ); REM; ( I^2 = 99% )</td>
<td>( \chi^2 = 1.06; P = 0.30; I^2 = 0% )</td>
<td></td>
</tr>
<tr>
<td>S1 Major surgery</td>
<td>7 (388)</td>
<td>10.51 (2.82, 18.20); ( P = 0.007 ); REM; ( I^2 = 99% )</td>
<td>( \chi^2 = 0.07; P = 0.80; I^2 = 0% )</td>
<td></td>
</tr>
<tr>
<td>S2 Minor surgery</td>
<td>9 (329)</td>
<td>6.00 (2.18, 9.82); ( P = 0.002 ); REM; ( I^2 = 72% )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 DSST and EAS</td>
<td>7 (261)</td>
<td>6.66 (−3.42, 16.74); ( P = 0.20 ); REM; ( I^2 = 72% )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 Mini-mental state</td>
<td>10 (496)</td>
<td>8.15 (2.71, 13.60); ( P = 0.003 ); REM; ( I^2 = 98% )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DEX, dexmedetomidine; DSST, digital symbol substitution test; EAS, emergence agitation score; REM, Random effects model.
Fig. 2 A forest graph showing the results of a meta-analysis of studies which examined the neurocognitive effects of dexmedetomidine against controls or comparators in healthy individuals. Study identities follow comparator (Alf, alfentanil; M, midazolam) and neurocognitive assessment tool name (DSST, digital symbol substitution test; TMT, trail making test).

Table 2 Important features of the method used for the present study

| Literature search | Databases searched: Medline/PubMed, Embase, Scopus, CINAHL, Ovid SP, EBSCO, Cochrane library and Google Scholar; Literature search Databases searched: Medline/PubMed, Embase, Scopus, CINAHL, Ovid SP, EBSCO, Cochrane library and Google Scholar; | MeSH terms and keywords: Dexmedetomidine, analgesia, anesthesia, surgery, perioperative, postoperative, intraoperative, premedication, cognitive dysfunction, cognition, neurocognitive, brain function, delirium, emergence agitation, confusion, adapted cognitive assessment (ACE), digital symbol substitution test (DSST), confusion assessment method for ICU (CAM-ICU), mini-mental state examination (MMSE) etc. | Search Period | Search encompassed original research papers published between 1980 and December 2014. | Type of studies | RCTs which compared perioperative use of dexmedetomidine with saline or comparator anesthetic/s and used a valid diagnostic tool for the assessment of neurocognitive function before and after surgery/anesthesia. | Participants | Surgical or ICU patients | Interventions included | Studies providing baseline and at least one post-anesthesia time point data regarding the effect of perioperative use of dexmedetomidine and control or comparator on postoperative/post-anesthesia neurocognitive function as continuous variables. | Interventions excluded | Studies providing information as incidence of postoperative neurocognitive dysfunction but not as continuous variable data; retrospective studies and case reports/series; studies not using a valid neurocognitive assessment tool; and studies providing information inadequate for meta-analysis. | Outcomes of interest | Scores of valid neurocognitive function diagnostic tools including ACE, CAM-ICU, DSST, MMSE etc. | Trial quality | The Cochrane Collaboration Risk of Bias Assessment Tool for the assessment of RCTs [41]. The assessment of publication bias was made by visual examination of asymmetry of the funnel plots. | Data extraction | Independently by two authors. Inter-rater reliability (Cohen kappa): = 0.94 | Meta-analysis method | Mean differences under fixed- and random-effects models (FEM and REM, respectively). The overall effect of treatment was a weighted average of the inverse variance adjusted individual effects. Significance of difference between groups was tested by two-tailed z test. Metaregression analyses were performed in Stata. | Sub-group analyses | Subgroups: Comparator vs controls, MMSE vs non-MMSE neurocognitive assessment tool utility, and major vs minor surgery. Each member of subgroup pair was first meta-analyzed and then the effect sizes of subgroup pair were subjected to Chi squared test for examining the significance of difference. | Heterogeneity | $I^2$ index used to assess between-study heterogeneity. Comparisons with $I^2 > 50\%$ were studied under REM and sensitivity analyses were performed to investigate the source of heterogeneity. | Software | RevMan (Version 5.3; Cochrane Collaboration)/Stata 12 SE (Stata Inc., College Station, TX, USA) |

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DEX</th>
<th>COMP</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Angst 2004 Alf/TMT</td>
<td>-58</td>
<td>31</td>
<td>6</td>
<td>-22</td>
</tr>
<tr>
<td>Angst 2004 TMT</td>
<td>-58</td>
<td>31</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hall 2000 DSST</td>
<td>-17</td>
<td>25</td>
<td>7</td>
<td>-1.44</td>
</tr>
<tr>
<td>Mattila 1991 DSST</td>
<td>0.69</td>
<td>29</td>
<td>6</td>
<td>0.67</td>
</tr>
<tr>
<td>Mattila 1991 Mida/DSST</td>
<td>0.69</td>
<td>29</td>
<td>6</td>
<td>50.66</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>31</td>
<td>55</td>
<td>160.0%</td>
<td>-12.72</td>
</tr>
</tbody>
</table>

Heterogeneity: $T^2 = 1662.30; \chi^2 = 43.22, df = 4 (P < 0.00001); I^2 = 91\%$

Test for overall effect: $Z = 0.69$ (P = 0.51)

Mean difference under median, major surgery, or MMSE vs comparator treated patients in the post-anaesthesia period. How-

studies which utilized any neurocognitive assessment tool other than MMSE revealed non-significant difference between dexmedetomidine- and control-/comparator-treated patients in neurocognitive performance (mean difference: 6.66 [-3.42, 16.74]; $P = 0.20$; REM) which was not similar to the outcomes of a meta-analysis of the studies with MMSE tool utilization (mean difference: 8.15 (2.71, 13.60); $P = 0.003$; REM; Fig. S3). In other submeta-analyses, no significant difference was noted when studies with major surgery and studies with minor surgery were meta-analyzed separately (Fig. S4).

In order to examine the significance of difference between the members of subgroup pairs, effect sizes were tested with the Chi squared test. However, no significant differences could be noted between subgroups — age over vs under 60, dexmedetomidine dose of over vs under median, major vs minor surgery, or MMSE vs non MMSE neurocognitive assessment (Table 1).

No significant associations were noted in the meta-regression analyses performed to assess the relationship of age and dexmedetomidine maintenance dose with the neurocognitive performance of dexmedetomidine treated patients (age: coefficient 0.222; standard error 0.221; $P = 0.331$; and dexmedetomidine dose: coefficient $-1.812$; standard error 20.44; $P = 0.931$).

**DISCUSSION**

In the present study, the meta-analyses were based on the mean differences in the percent changes from the baseline in the post-infusion neurocognitive performance between dexmedetomidine-and comparators-/saline-treated patients. Dexmedetomidine treatment was associated with significantly better neurocognitive function in comparison with saline treated controls as well as comparator treated patients in the post-anaesthesia period. How-

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ever, in the submeta-analyses, neurocognitive assessment with tools other than MMSE, and patients’ age under 60 years were not associated with significantly better performance against controls/comparators. Additionally, in young (24–26 years of age) healthy individuals, outcomes were not significantly different between dexmedetomidine and controls/comparators when they were infused dexmedetomidine experimentally.

Overall, these results are similar to a meta-analysis of risk ratios carried out by Pasin et al., who found that dexmedetomidine treatment was associated with reduced incidence of delirium, agitation and confusion in comparison with both saline treated or comparator anaesthetic treated patients. Pasin et al. used studies with incidence (binary) data, whereas, we have meta-analyzed studies with continuous data. Whereas, neurocognitive assessment was carried out mainly with CAM-ICU in their eligible studies, in our meta-analysis, MMSE is the most utilized tool; besides all included studies used a valid instrument for neurocognitive assessment.

An important finding of the present study is that dexmedetomidine treatment (in comparison with controls and comparators) was not associated with significantly better neurocognitive performance in patients under 60 years of age. However, meta-regression analyses could not find any significant relationship between age and neurocognitive performance of the dexmedetomidine treated patients. Perioperative dexmedetomidine is also associated with significant stress alleviating (cortisol reducing) properties and significant reductions proinflammatory cytokines; both the effects can be more beneficial in the elderly. Whether these results suggest that dexmedetomidine is more effective in elderly patients is subject to further investigations with larger datasets.

Age is identified as a major risk factor for long-term cognitive impairment following a surgery in a sample of over one thousand patients.

In the meta-analysis of Pasin et al., dexmedetomidine treatment was also associated with better neurocognitive performance in comparison to midazolam. This is also comparable to the outcomes of a submeta-analysis of the present study (dexmedetomidine vs comparators), as in this comparison, five out of six studies compared dexmedetomidine against midazolam and the overall results favored dexmedetomidine. Drug interactions may also play a role in the effectiveness of dexmedetomidine. In rat, synergistic effects of dexmedetomidine with benzodiazepines are reported. However, Smiley et al. infused dexmedetomidine intraoperatively and compared with dexmedetomidine plus midazolam but could not find any synergistic relationship between dexmedetomidine and benzodiazepine rather in the post-loading assessment, DSST scores were significantly higher in dexmedetomidine group than in the dexmedetomidine-midazolam group.

According to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines, whereas, dexmedetomidine use should be preferred over the benzodiazepines for lower risk of delirium, preference over propofol is not declared. In comparison with midazolam and propofol, dexmedetomidine offers limited cost-effective benefit in terms of quality adjusted life-years despite majority of studies report that dexmedetomidine reduced the total hospital costs and the ICU costs.

Clinical heterogeneity of the sample population can also impact the results of a meta-analysis examining the dexmedetomidine’s efficacy in overcoming post-anesthesia neurocognitive dysfunction. Besides age, duration of delirium, severity and
type of surgery, preoperative benzodiazepines use, low education level, type, trauma, duration of surgery, preoperative delirium or coma, dementia, hypertension. Acute Physiology and Chronic Health Evaluation II score, mechanical ventilation, and metabolic acidosis are also recognized as risk factors for postoperative neurocognitive dysfunction. In the mechanically ventilated ICU patients, duration of delirium has been found to be a modifiable predictor of cognitive dysfunction a year later. In a prospective observational study of 1359 post-anesthesia care unit patients of which 4.7% developed delirium, preoperative benzodiazepine use, breast and abdominal surgery and longer duration of surgery were noted as predictors of increased risk of delirium, whereas, history of illness and long-term treatment by antidepressants decreased the risk. High statistical heterogeneity in some comparisons of the present study may underlie above-mentioned factors of clinical and methodological heterogeneity.

In this meta-analysis of mean differences in the percent change from baseline in neurocognitive performance following anaesthesia and mechanical ventilation, dexmedetomidine treatment was associated with significantly better performance in comparison with saline- or comparator anaesthetic-treatments. However, there can be impact of the type of neurocognitive assessment tool on the overall findings. More randomized data in future trials will refine the evidence attained herein.

METHOD

This study was performed by following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Important features of the method are presented in Table 2.

REFERENCES
