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Sedation

Survival benefits of dexmedetomidine used for sedating septic patients in intensive care setting: A systematic review

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ABSTRACT

Purpose: The aim of this systematic review was to evaluate the effectiveness and safety of dexmedetomidine used for sedation of patients with sepsis.
Methods: We searched Medline, Scopus, TRIP and CENTRAL, DART, OpenGrey, and ProQuest without applying any language filter up to July 15, 2015. Two of the authors independently reviewed search results for irrelevant and duplicate studies and extracted data and assessed methodological quality of the studies. We used tabulation to synthesize the findings of the studies and transformed data into a common rubric and calculated a weighted treatment effect across studies using Review Manager.
Results: We found 124 references in 7 databases, and after exclusion of irrelevant and duplicate studies, 6 studies with total number of 242 patients with sepsis were included. The risk ratio for 28-day mortality was 0.49 (95% confidence interval, 0.24-0.99; $P = .05$) for the dexmedetomidine group vs the control group. The weighted mean difference for the length of stay in the intensive care unit was 1.54 (95% confidence interval, −1.73 to 4.81; $P = .36$). No adverse effect including hypertensive, hypotensive, or bradycardia response was reported in any studies.
Conclusion: In a small group of studies of patients with sepsis, dexmedetomidine improved short-term mortality compared with other sedatives without affecting the intensive care unit length of stay. Further studies are warranted to confirm whether using this particular agent improves sepsis outcomes in comparison to other commonly used sedating agents.

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1. Introduction

Septic shock is a life-threatening condition that results from catastrophic effects of an exaggerated immune response to infectious agents [1–3]. This systemic immune response leads to activation of inflammatory, coagulation, and fibrinolysis cascades and consequently leads to collateral tissue damage and multiple organ failure [2,4,5]. On the other hand, the compensatory anti-inflammatory response paves the way for secondary infections [4]. In the United States, 2% of patients admitted to the hospital have sever sepsis [4]. Worldwide, there are up to 19 million cases of severe sepsis each year, and this incidence is increasing by 8.7% per year [1,4,6–8]. Recent advances and breakthroughs in bundle care significantly decreased risk of immediate death associated with severe sepsis and septic shock, and as a result, imminent death rate declined from 80% to 20%-30% [1,4].

In view of decreased mortality, support of organ function has gained higher significance in the intensive care units (ICUs) [1,2]. Sepsis and septic shock commonly result in cardiovascular and respiratory compromise and central nervous system dysfunction [1,2,4]. Clinical picture of severe sepsis is often complicated with acute respiratory distress syndrome that necessitates mechanical support of ventilation [1,6]. Proper sedation is often a necessity in care of patients with sepsis in need of mechanical ventilation (MV) to reduce the stress and anxiety associated with tracheal intubation and other invasive interventions [1,2,4]. The choice of such sedative agent is critically important as patients with sepsis are generally in shock and extremely vulnerable for cardiovascular compromise [6]. Traditionally, γ-aminobutyric acid (GABA) receptor agonists such as benzodiazepines and propofol are commonly administered sedative agents in the ICU [6,9]. Recently, studies have highlighted sedative and analgesic properties of selective α_2 receptor agonists such as dexmedetomidine [10,11]. After its binding

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to transmembrane G protein adrenoreceptors, dexmedetomidine inhibits protein kinase A and leads to phosphorylation of downstream enzymes such as adenylate cyclase [12]. Hyperpolarization of noradrenergic neurons in the locus ceruleus mediates the sedative effects of dexmedetomidine, whereas its analgesic effect is a result of modulation of pain impulses in the noradrenergic pathways in the posterior horns of the spinal cord [7,8,12].

Limited but increasing evidence suggests that dexmedetomidine has a promising future as a sedative agent in the intensive care setting considering its excellent sedative and analgesic properties with wider safety margin due to the lack of suppressive effects on respiration [12,13]. Dexmedetomidine seems to have effects on apoptosis and modulation of the immune system which might be particularly important and play a critical role in the pathogenesis of sepsis [7,14]. On the other hand, hypotension and bradycardia, the most common adverse effects of dexmedetomidine, could influence hemodynamic stability in patients with septic shock [15,16]. Therefore, despite extensive research, its potential benefits and risks in patients with sepsis remain a controversy. The aim of the systematic review was to evaluate the effect of dexmedetomidine on the duration of ICU stay and 28-day mortality of patients diagnosed as having sepsis, severe sepsis, or septic shock according to the guidelines of Border of Immune Tolerance Education and Research Network (BITERN) and Cochrane collaboration.

2. Methods

The methods described in this systematic review were in accordance with BITERN guidelines and general methods recommended by Cochrane collaboration.

2.1. Criteria for considering studies for this review

In this review, we included all clinical trials (irrespective of randomization and blinding) investigating dexmedetomidine (irrespective of modes of administration and all variations of dosage, frequency, and duration) in patients with sepsis, severe sepsis, or septic shock (irrespective of age, sex, or race) according to inclusion criteria stated in the protocol (Supplementary Appendix 1).

2.2. Search methods for identification of studies

One author conducted the primary search process on July 15, 2014, in Medline, Scopus, TRIP and CENTRAL databases (as databases for journal article) and DART, OpenGrey, and ProQuest (as databases for gray literature) according to the search strategies stated in the protocol (Supplementary Appendix 1). We did not apply any language filter or date restriction and we updated the search process in Medline, Scopus, CENTRAL, ProQuest, DART, and OpenGrey databases up to July 15, 2015. In addition, the reference lists of articles identified were searched for relevant trials. Citations from all databases were imported into an Endnote library (version X6; Thomson Reuters, New York, NY). In the Endnote library, we used the "Find Duplicates" feature of Endnote software to identify the duplicates among citations. Then 2 of the authors independently reviewed the title and abstract of the remainders of search results for irrelevant studies and obvious irrelevant studies were excluded. We retrieved the full text of the remaining citations for further screening and data collection process.

2.3. Data collection and quality assessment

Two reviewers independently examined the full text of the articles for eligibility according to the inclusion criteria (Supplementary Appendix 1). Reviewers resolved ambiguity or any disagreement regarding the eligibility of studies through either discussion or consultation with a third author. They excluded ineligible studies along with documenting reasons for exclusion. Two reviewers independently extracted data from articles to predesigned and pretested data extraction forms in Microsoft Excel spreadsheets (version 2010; Microsoft Corporation, Redmond, WA). They also assessed methodological quality of the studies independently by using a modified version of Cochrane "Risk of bias" tool on the following domains (developed by scientific committee of BITERN; Supplementary Appendix 2):

1. Random sequence generation (selection bias for controlled trials)
2. Allocation concealment (selection bias for controlled trials)
3. Generalizability of the findings to the target population (selection bias for trials without control)
4. Blinding of participants and personnel (performance bias)
5. Blinding of outcome assessment (detection bias)
6. Incomplete outcome data (attrition bias)
7. Selective reporting (reporting bias)

Each domain was judged to be "low risk" of bias, "high risk" of bias, or "unclear risk" of bias. Any disagreements between data collectors were resolved through either discussion or consultation with a third author.

Furthermore, the quality of the studies was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology as described elsewhere [17]. This methodology is widely accepted and used by the guideline writing committees, which includes assessment of the evidence whether it addresses same population, intervention, comparison, and outcome. In brief, the quality of evidence was graded as "low," "moderate," or "high" and the results were interpreted accordingly. Mortality rate with 28 days was the main primary outcome for this study which was invariably addressed within all studies. However, later days of MV and ICU length of stay were added to the existing protocol, retrospectively.

2.4. Evidence synthesis

We undertook systematic approaches to synthesize the findings of the studies because there was clinical heterogeneity in the included studies. We used tabulation and textual description to synthesize the findings of the studies. In addition, for all studies, we transformed data into a common rubric and presented dichotomous outcomes as risk ratio (RR) and 95% confidence interval (CI), and continuous outcomes as mean difference (MD) and 95% CI. All conversions were done using Review Manager (Version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark; the Cochrane Collaboration, 2014). For missing data, we considered statistics that allow for calculation of missing data in the article, or in some cases, we contacted the corresponding author.

When between-study heterogeneity was allowed, we calculated a weighted treatment effect across studies using Review Manager. We assessed between-study heterogeneity by the χ^2 statistic and its P value, and the extent of inconsistency using the I^2 statistic. We considered a P value less than .1 and $I^2 > 40\%$ as indicating significant between-study heterogeneity. In case of significant heterogeneity, we did meta-analysis using a random-effects meta-analysis; otherwise, a fixed-effect model was used. We expressed the results as RRs with 95% CI for dichotomous outcomes, and MD with 95% CI for continuous outcomes.

3. Results

3.1. Description of studies

We found 124 references by recruiting the search strategy in 7 databases (Fig. 1). We did not retrieve any studies in reference lists of the main articles. After discarding duplicates, we identified 100 publications. In primary screening of titles and abstracts, 75 articles were excluded due to obvious irrelevancy of the topics. In secondary screening of full-text articles, 6 studies with a total number of 242 patients with sepsis or septic shock were identified and included in this systematic review (Table 1). Four studies included patients with either severe