Use of Dexmedetomidine in Liver Disease: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Dexmedetomidine is a sedative and analgesic medication that is frequently used postoperatively in children after liver transplantation, hepatic dysfunction and liver failure.

Objectives: The aim of this systematic review was to determine the role of dexmedetomidine in liver disease.

Methods: We systematically reviewed the literature from PubMed, Embase, Scopus, ProQuest, Web of Science, and The Cochrane Library from January 1980 to June 2019. The search strategy included a combination of Mesh and free keywords such as liver transplantation, liver diseases, liver failure, and dexmedetomidine.

Results: From a total of 741 articles, 7 studies were included in this systematic review. In the selected studies, a total of 218 patients in the control and treatment groups were studied. Based on the Fixed effect model, MAP changes in the intervention group were 1.89 units less than the control group, which was not statistically significant (pooled mean difference = -1.89, 95% CI: -6.28 to 2.5, P value = 0.39).

Conclusions: DEX injection prior to anesthesia potentially had a protective effect on liver and intestinal function during hepatectomy with vascular occlusion.

Keywords: Dexmedetomidine, Liver Disease, Liver Transplantation

1. Introduction

The liver plays an important role in metabolism of carbohydrates, proteins, lipids, drugs, and toxins.

The slow and long-term process of liver disease results in progressive increase in number of patients with hepatic disorders. Chronic liver disease includes a wide range of liver pathologies from inflammation to cirrhosis. Cirrhosis is characterized by expansion of regenerative nodules and fibrous bands in response to chronic liver injury, leading to end-stage liver disease. Special attention is needed to choose the best matching pharmacokinetic and pharmacodynamic treatments in patients with liver disease (1).

Dexmedetomidine (DEX) is the new α2-adrenoreceptor agonist that has a complete metabolism in the liver and almost complete excretion in urine (2). This drug has a fast onset of action and minimal side effects. It also has a synergistic effect when combined with most anesthetic drugs. Its side effects include bradycardia, vasoconstriction, and mild respiratory depression (3). Additionally, DEX is also used as an anesthetic drug and has sedative, analgesic and anti-inflammatory effects (4). It can be administered with both intravenous and intranasal methods, and the studies have shown that in addition to its pharmacodynamic and pharmacokinetic features, its analgesic and sedative effects are the same in both methods (5). The DEX dosage in patients with liver failure needs to be adjusted (6). It also needs to be adjusted in patients with obstructive jaundice due to its decreased volume of distribution (7).

Lower doses of DEX have protective effect while high doses (10 µg/kg) have negative effects on the liver tissue which can be minimized by simultaneous administration of 100 mg/kg of vitamin C (8). In patients with irritable bowel disease (IBD), the extra-intestinal manifestations may include liver inflammation. In animal models of IBD, DEX prescription reduces ultra-structural and
histopathological damage of liver (9). Administration of DEX exerted protective effects against hepatic ischemia-reperfusion injury (IRI) in adult living donor liver transplantation. It results in suppression of ICAM-2, improved scores of histopathologic assessment, and augmentation of live function tests after surgery (10). Patients with liver transplantation, have a high risk of post-surgery delirium. Administration of DEX for more than 3 days with cycling may be useful in delirium prevention in these patients (11). In children undergoing liver transplantation with post-surgery myocardial or brain injury, DEX can be used to reduce the injury (12, 13). In patients with mild liver dysfunction undergoing laparotomy, DEX is used in combination with propofol and remifentanil for general anesthesia (14). In cirrhotic patients, DEX usage as an anesthetic drug results in improvement of dynamic stability, reduction in stress response, and reduction of inflammation rate, without having adverse effect on immunologic functions, which has a significant clinical value (15).

2. Objectives

Considering the mentioned studies and to the best of our knowledge, no systematic review has been conducted in this field. In this respect, our aim in this study is to conduct a systematic review of DEX effects in patients with liver disorders.

3. Methods

This systematic review and meta-analysis follows the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist.

3.1. Literature Search

Embase, PubMed, Ovid, Scopus, ProQuest, Web of Science, The Cochrane Libraries and Google Scholar were searched to identify studies that reported the results of dexmedetomidine administration on any form of hepatic injury like hepatic reperfusion injury. Using the Medical Subject Headings (MeSH) and Emtree keywords including "Liver Transplantation", "Liver Diseases", "Chronic Hepatitis", "Cirrhosis", "Hepatectomy", "Liver Failure", "Dexmedetomidine" and combining them with Boolean Operators, studies which were published in English from January 1980 to June 2019 were investigated and other sources including grey literature and articles presented in congresses were also searched. Additional information about the search strategy is presented in the PRISMA flow diagram in Figure 1.

3.2. Study Selection

The inclusion criteria for this study were as follows:
1- Randomized control trials (RCTs) investigating the role of dexmedetomidine in hepatic patients
2- Articles published in English from January 1980 to June 2019
3- Articles with access to their full texts
The exclusion criteria were considered to be as follows:
1- Non-randomized controlled trials
2- Unavailability of the full text of the articles
The results were imported to the Endnote X8 software to remove the duplicates and organize the studies.

3.3. Methodological Quality

Assessment of methodological quality and the risk of bias of enrolled randomized controlled trials were performed using Cochrane checklist to evaluate the randomization sequence, allocation concealment, determination of whether blinding was implemented for participants or outcome assessors, and evidence of selective reporting or other notable biases. Accordingly, articles were categorized into 3 groups: "low risk of bias/L" “high risk of biases/H" or “unclear risk of bias/U".

3.4. Data Extraction

Two independent reviewers, H.S and K.SH, selected the studies following three steps; first title of all the studies was reviewed, then abstract and full text of the articles was investigated and finally, risk of bias was evaluated to exclude all the irrelevant studies. Any disagreement between reviewers was resolved by consulting with a third evaluator, MG.

Extracted data included first author’s name, year of publication, type of the study, sample size, mean age, weight, sex of the participants, baseline MAP, postoperative MAP, dosage of the drug, condition, effects and adverse effects of the drug.

3.5. Data Analysis

Statistical analysis was performed using CMA version 0.3. Assessment of heterogeneity between studies was done by application of Cochrane’s Q statistic (heterogeneity < 0.10 suggesting statistical significance) and the I² statistic. I² < 50% was considered to show no statistical heterogeneity and fixed-effect model was used, on the other hand, I² ≥ 50% or P value < 0.05 indicated significant heterogeneity, therefore required a random effect model for analysis. P value < 0.05 was considered to be statistically significant.
4. Results

4.1. Search Results and Study Characteristics

In the systematic search, 741 articles were identified. Among them, 92 articles were duplicate and 617 were excluded after reviewing the titles and abstracts. After screening the full text of the articles, 22 articles were excluded. Finally, seven studies conforming to the inclusion criteria entered this systematic review. The flowchart for the articles identified and entered into the study is shown in Figure 1. The characteristics of the included studies are provided in Table 1.

4.2. Participant Characteristics

In this study, 4 studies were finally entered into a meta-analysis. In the selected studies 218 patients in the both control and intervention groups were studied. The mean ± standard deviation of the participants’ age was 48.04 ± 3.97 in the control group and 46.82 ± 3.65 in the intervention group.
α is the selective agonist of status of patients during and after anesthesia. This drug patients with multiple cirrhosis could improve the clinical catecholamines (16). Wang L. determined that DEX in pa-

stand, it may play a role in decreasing the plasma levels of other organs such as the intestines. Although the mech-

anism of protective effects of DEX is not yet fully under-

stood, it can suppress the secretion of adrenaline and thereby reduces tissue ischemia.

3- Stimulation of the α2-adrenergic receptor which re-

duces intestinal and myocardial ischemia.

4- A dose of 0.8 μg/kg/h DEX reduces the concentration of isoflurane, inhaled doses of fluoride and reduces fentanyl consumption during surgery.

5- Reduces the number of neutrophils and subsequently reduces endothelin-1 and reduces protease by re-

ducing the level of ICAM-1 (an important molecule in the adhesion of leukocytes during the migration of leukocytes to the inflammation site), which protects organs like intestine and kidney from ischemia while protecting the trans-

planted organ [10].

Sayed and Yassen showed that DEX can be considered as an adjunctive therapy and have an effective role in sta-

bilizing the hemodynamic symptoms of patients, reduc-

ing the dosage of inhalational desflurane and fentanyl con-

sumption without affecting the depth of anesthesia, reduc-

ing oxygen consumption and reducing production of CO2. Due to the sympatholytic effect of DEX, the sympathoad-

renal response to tracheal intubation of these patients is reduced and intubation is facilitated. Because of its anal-

gesic effect, it provides better analgesia during and after surgery, reduces HR and MAP during intubation and dur-

ing anesthesia due to reduced stress response, and there-

fore is effective in stabilizing hemodynamic symptoms in patients. It decreases oxygen consumption throughout the tissues especially the transplanted tissue by a reduc-

ion in sympathetic activity and subsequent reduction of total body metabolism, and due to its antinociceptive ef-

fect and indirect effect on sedation and neuromuscular block (17).
5.1. Conclusions
Injection of DEX prior to anesthesia potentially had a protective effect on liver and intestinal function during hepatectomy with vascular occlusion. While DEX injection through anesthesia in cirrhotic patients stabilized hemodynamic symptoms and reduced the stress response, it also reduced the level of inflammation without affecting the function of the immune system. Reducing the consumption of fentanyl and desflurane during anesthesia, DEX injection through anesthesia in patients who required liver transplants is effective in stabilizing hemodynamic symptoms, reducing tissue ischemia, and improving liver function.

Footnotes

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References
1. Soleimanpour H, Safari S, Shahsavari Nia K, Sanaie S, Alavian SM. Opioid drugs in patients with liver disease: A systematic review. Hepat Mon. 2016;16(4). e23636. doi: 10.5812/hepatmon.32636. [PubMed: 27257423]. [PubMed Central: PMC4887963].
2. Afshani N. Clinical application of dexmedetomidine. S Afr J Anaesthesiol Analg. 2014;16(3):50-6. doi: 10.1080/22201773.2014.10872681.
3. Bagatini A, Gomes CR, Masella MZ, Rezer G. [Dexmedetomidine: pharmacology and clinical application]. Rev Bras Anestesiol. 2002;52(5):606-17. Portuguese. doi: 10.1590/S0034-70942002000500002. [PubMed: 19475232].
4. Bagatini A, Volquind D, Rosso A, Trindade RD, Spllettstoesser FC. [Dexmedetomidine as adjuvant drug for wake-up test during scoliosis correction surgery: case report]. Rev Bras Anestesiol. 2004;54(2):247-51. Portuguese. doi: 10.1590/S0034-70942004000200002. [PubMed: 19477132].
5. Li A, Yuen VM, Goulay-Dufay S, Kwok PC. Pharmacokinetics and pharmacodynamics of dexmedetomidine. Drug Dev Ind Pharm. 2016;42(12):1917-27. doi: 10.1080/03639045.2016.1232727. [PubMed: 27595299].
6. Cunningham F, Baughman V, Tonkovich L, Lam N, Layden T. Pharmacokinetics of dexmedetomidine (DEX) in patients with hepatic failure (HF). Clin Pharmacol Ther. 1999;65(2):128. doi: 10.1016/s0009-9236(99)80045-9.
7. Song JC, Gao H, Qiu HB, Chen QB, Cai MH, Zhang MZ, et al. The pharmacokinetics of dexmedetomidine in patients with obstructive jaundice. Bratisl Lek Listy. 2016;117(1):36–40. doi: 10.4149/BLL_2016_008. [PubMed: 26810168].
8. Sheng M, Hongyin DU, Wenli YU, Weng Y, Sun Y. [Effect of dexmedetomidine on myocardial injury in pediatric patients undergoing living-related liver transplantation]. Chinese J Anesthesiol. 2017;37(2):263-6. Chinese.
9. Sun Y, Hongli Y, Wenli YU, Jia L, Weng Y, Wang F, et al. [Effect of dexmedetomidine on postoperative brain injury in pediatric patients undergoing living-related liver transplantation]. Chinese J Anesthesiol. 2017;37(2):251-4. Chinese.
14. Cui M, Zhang J, Meng F. [Optimum dose of dexmedetomidine combined with propofol and remifentanil for anesthesia during laparotomy in patients with mild liver dysfunction]. Chinese J Anesthesiol. 2013;33(8):959-62. Chinese.

15. Wang L, Zhang A, Liu W, Liu H, Su F, Qi L. Effects of dexmedetomidine on perioperative stress response, inflammation and immune function in patients with different degrees of liver cirrhosis. Exp Ther Med. 2018;16(5):3869-74. doi: 10.3892/etm.2018.6665. [PubMed: 30444066]. [PubMed Central: PMC676194].

16. Wang ZX, Huang CY, Hua YP, Huang WQ, Deng LH, Liu KX. Dexmedetomidine reduces intestinal and hepatic injury after hepatectomy with inflow occlusion under general anaesthesia: A randomized controlled trial. Br J Anaesth. 2014;112(5):805-10. doi: 10.1093/bja/aeu132. [PubMed: 2477805].

17. Sayed E, Yassen KA. Intraoperative effect of dexmedetomidine infusion during living donor liver transplantation: A randomized control trial. Saudi J Anaesth. 2016;10(3):288-94. doi: 10.4103/1658-354X.174944. [PubMed: 2735383]. [PubMed Central: PMC4968812].

18. Rodrigues AD, Roberts EM. The in vitro interaction of dexmedetomidine with human liver microsomal cytochrome P4502D6 (CYP2D6). Drug Metab Dispos. 1997;25(5):651-5. [PubMed: 9152607].

19. Feng J, Yao W, Zhang Y, Xiang AP, Yuan D, Hei Z. Intravenous anesthetics enhance the ability of human bone marrow-derived mesenchymal stem cells to alleviate hepatic ischemia-reperfusion injury in a receptor-dependent manner. Cell Physiol Biochem. 2018;47(2):556-66. doi: 10.1159/000489889. [PubMed: 29794450].

20. Zhu X, Zhou JH, Li GW, Zhou WY, Ou SS, Xiao YX. Dexmedetomidine protects liver cell line L-02 from oxygen-glucose deprivation-induced injury by down-regulation of microRNA-371. Eur Rev Med Pharmacol Sci. 2018;22(19):4607-16. doi: 10.26355/eurrev_201810_16065. [PubMed: 30338822].

21. Arcangeli A, D’Alo C, Gasparri R. Dexmedetomidine use in general anaesthesia. Curr Drug Targets. 2009;10(4):687-95. doi: 10.2174/13894500978978982432. [PubMed: 19702517].

22. Tufek A, Tokgoz O, Alisumanoglu I, Alabalik U, Evliyaoglu O, Ciftci T, et al. The protective effects of dexmedetomidine on the liver and remote organs against hepatic ischemia reperfusion injury in rats. Int J Surg. 2013;11(1):96-100. doi: 10.1016/j.ijsu.2012.12.003. [PubMed: 22669446].

23. Sahin T, Begec Z, Toprak HJ, Polat A, Vardi N, Yuce A, et al. The effects of dexmedetomidine on liver ischemia-reperfusion injury in rats. J Surg Res. 2013;183(1):385-90. doi: 10.1016/j.jss.2012.11.034. [PubMed: 23221519].

24. Yeh YC, Sun WZ, Ko WJ, Chan WS, Fan SZ, Tsai JC, et al. Dexmedetomidine prevents alterations of intestinal microcirculation that are induced by surgical stress and pain in a novel rat model. Anesth Analg. 2012;115(3):46-53. doi: 10.1213/ANE.0b013e318253936c. [PubMed: 22504209].

25. Kocoglu H, Ozturk H, Ozturk H, Yilmaz F, Gulcu N. Effect of dexmedetomidine on ischemia-reperfusion injury in rat kidney: A histopathologic study. Ren Fail. 2009;31(1):70-4. doi: 10.1080/0886020802546487. [PubMed: 1942881].

26. Hall SR, Wang L, Milne B, Hong M. Central dexmedetomidine attenuates cardiac dysfunction in a rodent model of intracranial hypertension. Can J Anaesth. 2004;51(10):1025-33. doi: 10.1007/BF03018493. [PubMed: 15574556].

27. Can M, Gul S, Bektaş S, Hanci V, Aktikoglu S. Effects of dexmedetomidine or methylprednisolone on inflammatory responses in spinal cord injury. Acta Anaesthesiol Scand. 2009;53(8):1068-72. doi: 10.1111/j.1399-6576.2009.02099.x. [PubMed: 19519725].
| First Author | Year | Country | Type of Study | Sample Size | Mean Age | Weight | Gender (Male/Female) | Dosage | Condition | Adverse Effects |
|--------------|------|---------|---------------|-------------|----------|--------|---------------------|--------|-----------|-----------------|
| Wang         | 2014 | China   | RCT           | 22          | 58.4 ± 10.3 | 60.9 ± 9.6 | 16.6 | 1-0.3 mg/kg/h | Elective hepatectomy with inflow occlusion |
| Wang         | 2018 | China   | RCT           | 47          | 46.85 ± 46.56 | 26.2 ± 28.03 | 1-0.5 µg/kg | Liver Cirrhosis | Preoperative agitation |
| Fayed        | 2016 | Egypt   | RCT           | 20          | 52.47 ± 5.8 | 50.6 ± 7.5 | 18.2 | 0.6 lg/kg/h | Hepatic ischemia-reperfusion injury (IRI) |
| Sayed        | 2016 | Egypt   | RCT           | 20          | 44.6 ± 3.5 | 43.3 ± 1.34 | 16.4 | 0.2-0.7 µg/kg/h | During living donor liver transplantation (LDLT) on the general anesthetic requirements, hemodynamics, oxygen consumption (VO2), and CO2 production (VCO2) infusion of DEX as an adjuvant in general anesthesia caused decreased requirement of Des and fentanyl in patients undergoing LDLT without compromising adequate depth of anesthesia |
| Rodrigues    | 1997 | USA     | In vitro      | 5           | 0.01 - 4.0 µM | 0.01-40 µM | Interaction of desmopressin with human liver microsomal cytochrome P450 (CYP) 3A4 (CYP3A4) |
| Feng         |      | China   | In vitro      | 44          | 1 µM | 1 µM | Hepatic ischemia-reperfusion injury |
| Zhu          | 2018 | China   | In vitro      | 5           | 5.4 µM | 5.4 µM | Ischemic liver injury |