



The Open Anesthesia Journal

Content list available at: <https://openanesthesiajournal.com>



SYSTEMATIC REVIEW

Perioperative Dexmedetomidine Infusion, as Opioid-Sparing Strategy, in Patients Undergoing General Anesthesia: A Systematic Review Protocol

Marco Fiore^{1*}, Aniello Alfieri¹, Maria B. Passavanti¹, Anna Battimelli¹, Alessia Gatani¹, Giuseppe Mangoni¹, Vittorio Simeon², Paolo Chiodini² and Maria C. Pace¹

¹Department of Women, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", 80138, Naples, Italy

²Department of Public, Clinical and Preventive Medicine, Medical Statistics Unit, University of Campania "Luigi Vanvitelli", 80138, Naples, Italy

Abstract:

Introduction:

Although there are multiple analgesia techniques, opioids remain the most widely used drug for pain control. Postoperative Nausea and Vomiting (PONV), sleepiness, respiratory, and gastrointestinal disorder are common complications of postoperative opioid use, which makes the decrease in opioid demand, through combination with non-opioid agents, desirable. Dexmedetomidine (DEX) is an α_2 -adrenergic agonist with sedative and anxiolytic effects. Recently, some studies proved the evidence of its notable opioid-sparing effect. Furthermore DEX, compared to opioids, seems to have the advantage of not inhibiting spontaneous breathing.

Aim:

This systematic review protocol aims to define the analgesic effect of perioperative DEX infusion and the cumulative opioid consumption of patients undergoing general anesthesia.

Methods:

The review will be conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement and the Cochrane recommendations for Systematic Reviews of Interventions.

Results:

The primary outcomes will be 1) The effect of DEX infusion, on pain control, compared to placebo or other treatments and 2) The opioid-sparing effect of DEX infusion compared to placebo or other treatments. The secondary outcome will be a) Respiratory depression, b) Hypotension requiring fluid infusion and/or amine, c) Bradycardia requiring vasoactive drugs, d) Needing of prolonged hospital stay, e) PONV and gastrointestinal disorders.

Conclusion:

A sub-analysis is planned for i) The type of surgery performed, ii) Patient's gender, iii) Patients age. If possible, a meta-analysis (including sub-analysis and sensitivity analysis for all assessed outcomes) will be performed. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach will be followed to create a Summary of Findings.

The Registration Number for this Systematic Review is CRD42018086687.

Keywords: Dexmedetomidine (DEX), Opioid consumption, Perioperative pain, Postoperative Nausea and Vomiting (PONV), Analgesic effect, Bradycardia.

Article History

Received: August 16, 2019

Revised: September 27, 2019

Accepted: October 28, 2019

1. INTRODUCTION

Frequently, the ineffective management of perioperative

pain can affect the length of hospital stay by increasing the risk of postoperative complications and reducing patient mobility [1]. Although there are multiple analgesia techniques, opioids remain the most efficient and most widely used drug for pain control. Postoperative Nausea and Vomiting (PONV), sleepiness, respiratory, and gastrointestinal disorder are common complications of postoperative opioid use, which makes

* Address correspondence to this author at the Department of Women, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Piazza Miraglia 2, 80138 Naples, Italy; Tel: +39 0815665180; Fax: +39 081455426; E-mail: marco.fiore@unicampania.it

the decrease in opioid demand, through combination with non-opioid agents, desirable. For example, some authors suggest that for the abdominal surgery, related itself with the risk of ileus, opioids should be used only when non-opioid drugs provide insufficient analgesia [2]. Dexmedetomidine (DEX) is an α_2 -adrenergic agonist, with a structure similar to clonidine but with relative specificity for α_2 -receptors over α_1 -receptors. The action on α_2 -adrenergic receptors in the locus coeruleus explains the sedative and anxiolytic effects of DEX, decreasing the sympathetic tone. DEX promote the substance P release in the dorsal horn of the spinal cord and provide its analgesic effects [3].

Chrysostomou *et al.* described that DEX administration gives analgesia and sedation showing benzodiazepine and opioid-sparing effect when used with anesthetic drugs [4]. Some studies proved the evidence of a notable opioid-sparing effect of DEX [5 - 7]. Furthermore, DEX, compared to opioids, seems to have the advantage of not inhibiting spontaneous breathing [8, 9].

This systematic review aims to define the analgesic effect of DEX when used during general anesthesia and the potential advantages of implementing this drug in balanced anesthesia. Moreover, DEX use could reduce the amount of opioids in general anesthesia, reducing opioid complications and side effects such as PONV, dizziness, constipation, physical dependence, tolerance, and respiratory depression [10].

As done in previous literature reviews, we will include all types of surgical procedures under general anesthesia [11]; this is the first protocol including all kind of surgery, instead of the previously published systematic review, focusing only on specific surgery such neurosurgery [12], cardiac surgery [13], or bariatric surgery [14]. Besides, this systematic review differs from the previously published review because it includes all age groups instead of the previously published review that considered only pediatric patients [15]. Again, this systematic review deals with the systemically use (intravenous) of DEX and not in loco-regional anaesthesia [16].

1.1. Objective

This review will evaluate the effect of perioperative DEX infusion on the cumulative opioid consumption of patients undergoing general anesthesia. We hypothesize that DEX use in the perioperative period could reduce the occurrence of opioid side effects, improve the patient's overall outcome, and decrease hospitalization time.

2. METHODS

We will conduct the review in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA- P) statement and the Cochrane recommendations for Systematic Reviews of Interventions [17, 18]. The review protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews, Registration Number CRD42018086687).

2.1. Types of Studies

This review will consider randomized controlled trials,

quasi-experimental studies, case-control studies, and cohort studies. The introduction of the systematic review will consider narrative reviews and expert opinion papers.

2.2. Types of Participants

The current review will include studies enrolling patients undergoing general anaesthesia with no limits on age and type of surgery. We will include studies that report the dosage of opioids administrated in the perioperative period and assessing pain intensity with all approaches available.

2.3. Types of Interventions

This review will evaluate the effectiveness of DEX use in general anaesthesia in order to control perioperative pain and the opioid-sparing effect.

2.4. Types of Outcome Measures

Each outcome of perioperative pain intensity: Categorical scales (*i.e.*, mild, moderate, severe), Visual Analogue Scales (VAS), Numerical Rating Scales (NRS), and well-validated verbal scales (*i.e.*, the Descriptor Differential Scale). Studies evaluating patients on treatment for chronic pain or that presents comorbidity needing analgesic therapy will be excluded. We define the perioperative period as inclusive of the preoperative time, operative time, and postoperative period (up to 48h after the surgery).

2.4.1. Primary Outcome Measures

1. The effect of DEX infusion on pain control, assessed with all approaches available, compared to placebo or other treatments.

2. The opioid-sparing effect of DEX infusion compared to placebo or other treatments. The different types of analgesic drugs will be compared using a conversion chart that lists equivalent doses of analgesics (analgesic drugs other than morphine will be converted to morphine equivalents).

2.4.2. Secondary Outcome Measures

1. Respiratory depression requiring ventilation and/or Intensive Care Unit (ICU) admission

2. Hypotension requiring fluid infusion and/or amine

3. Bradycardia requiring vasoactive drugs

4. Needing of prolonged length of hospital stay

5. PONV and gastrointestinal disorders

2.5. Search Methods for Identification of Studies

A three-step search strategy will be used with the aim to find only published studies: An initial search of MEDLINE will be undertaken with an analysis of the title and abstract words, and of the mesh terms used to describe the retrieved articles. This will inform the development of a search strategy that will be tailored for each information source. A proposed search strategy for PubMed is detailed in Table 1. The second step will be a search using all identified keywords and mesh terms, it will be started through all included databases (see below for the databases list). The third step will be the search

for additional eligible studies in the reference list of all retrieved articles.

Only studies published in English will be considered for inclusion in this review.

Table 1. Search strategy on PubMed (conducted on August 2019).

Search	Query	Records Retrieved
1	(general anesthesia[mesh] OR general an*) AND dexmedetomidine[mesh] AND (analgesics, opioid[mesh] OR analgesi* OR opioid*)	405

The databases to be utilized will be PUBMED, EMBASE, and The Cochrane Central Register of Controlled Trials (CENTRAL).

2.6. Data Collection and Analysis

2.6.1. Selection of Studies

Two authors will independently evaluate the titles and abstracts of potentially eligible studies. The full text of identified studies will be assessed in detail by two reviewers. The Reasons for exclusion of the studies that do not meet the inclusion criteria will be recorded and reported in the review. Any disagreements that arise between the two reviewers at each stage of the study selection process will be resolved through discussion with a third reviewer.

2.6.2. Data Extraction and Management

All identified citations will be loaded into Endnote X8.0 (Clarivate Analytics, PA, USA) and duplicate removed. Data will be extracted from included studies, using a standardized data extraction tool, by two independent reviewers; these data will include specific details about the populations, study methods, interventions, and outcomes of significance to the review objective. Any disagreements that arise between the reviewers will be resolved through the discussion with a third reviewer. The results of the search will be reported in full in the final report and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [17].

2.6.3. Measures of Treatment Effect

For dichotomous outcomes, Risk Differences (RDs) will be used either for primary or secondary outcomes. For each study, the proportion of patients with DEX infusion will be used to calculate RD and corresponding 95% Confidence Interval (CI) using a 2x2 table. The proportion of patients with DEX infusion also will be calculated for each study

2.6.4. Assessment of Methodological Quality

The included studies will be appraised for methodological quality independently by two authors. The reviewers will assess qualitative papers selected for retrieval for methodological quality prior to inclusion in the review. Study quality will be independently assessed by two authors, for the observational studies will be used the Newcastle-Ottawa

Quality Assessment Form and for the Randomized Controlled Trials (RCT) the Cochrane tool [18, 19]. Any disagreements between the reviewers will be resolved through discussion with a third reviewer.

2.6.5. Dealing with Missing Data

The authors of manuscripts will be contacted to request missing or additional data for clarification, where required.

2.6.6. Data Synthesis

Heterogeneity between studies will be assessed using Q statistic and I², which is the proportion of total variance observed between the studies attributed to the differences between studies rather than to sampling error. I² values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity, a *P*-value of Q statistic less than 0.10 will be considered significant. If overall heterogeneity will be significant, a random-effect model will be used, otherwise, a fixed-effect model will be used. Where statistical pooling will be not possible, the findings will be presented in a narrative form including tables and figures to aid in data presentation where appropriate.

Where quantitative pooling is not possible, the findings will be presented in narrative form.

2.6.7. Subgroup Analysis

A sub-analysis is planned for:

1. The type of surgery performed
2. Patient's gender
3. Patients age: Neonatal and infant (< 1-year old), Child and adolescent (1<year old<18), Adult (18< year old< 65, and Geriatric (> 65-year old).

2.6.8. Assessment of the Overall Quality of Evidence

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [20] approach will be followed and a Summary of Findings (SoF) will be created using GRADEPro GDT software. The SoF will present the following information where appropriate: Absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication bias of the review results. All primary outcomes will be included in the Summary of Findings.

3. RESULTS AND DISCUSSION

Despite different strategies in pain management, opioids remain the most widely used drug for pain control. Although their use is burdened by innumerable adverse events that are currently in the public domain. Recently, there is a great emphasis on limiting the use of opioids; on April 25th, the Food and Drug Administration (FDA) launched its newest campaign "Reduce the Risk" against the epidemic of opioid use [21]. The FDA focuses the campaign on women aged 35 to 64; This demographic target (gender and age) has led us to consider these two variables in the sub-analysis. So, the strength of this

review, beyond the methodology, [17 - 20] is the topic of opioid-sparing taking into account the gender and age of patients. The concerns about the limitations of our findings arise from the fact that there are few randomized controlled trials in the literature, which could make our results inconclusive.

CONCLUSION

Actually, there is a tendency to reduce the use of opioids due to the potential adverse effects related to their use. The attitude taken by anesthesiologists is the opioid administration in combination with other anesthetic drugs in order to reduce the amount of opioids in general anesthesia.

This systematic review will provide an important update on DEX use in general anesthesia, answering the question if the perioperative DEX infusion has an opioid-sparing effect balanced by a lower occurrence of adverse events.

LIST OF ABBREVIATIONS

CENTRAL	= The Cochrane Central Register of Controlled Trials
CI	= Confidence Interval
DEX	= Dexmedetomidine
FDA	= Food and Drug Administration
GRADE	= Grading of Recommendations, Assessment, Development and Evaluation
ICU	= Intensive Care Unit
NRS	= Numerical Rating Scales
PONV	= Postoperative Nausea and Vomiting
PRISMA- P	= Systematic Review and Meta- Analysis Protocols
PROSPERO	= The International Prospective Register of Systematic Reviews
RCT	= Randomized Controlled Trials
RDs	= Risk Differences
SoF	= Summary of Findings
VAS	= Visual Analogue Scales

AUTHORS' CONTRIBUTIONS

MF developed the idea for the review and is the guarantor of the review. MF and AA drafted the protocol. All authors made critical revisions for the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

STANDARD OF REPORTING

This review is in accordance with the Preferred Reporting Items for Systematic Review and Meta- Analysis Protocols (PRISMA- P) statement and the Cochrane recommendations for Systematic Reviews of Interventions.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This protocol was presented at the 41st congress of the Italian Association for the Study of Pain (AISD) and awarded as the best abstract presented.

REFERENCES

- [1] Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet* 2003; 362(9399): 1921-8. [http://dx.doi.org/10.1016/S0140-6736(03)14966-5] [PMID: 14667752]
- [2] Bonnet F, Marret E. Postoperative pain management and outcome after surgery. *Best Pract Res Clin Anaesthesiol* 2007; 21(1): 99-107. [http://dx.doi.org/10.1016/j.bpa.2006.12.007] [PMID: 17489222]
- [3] Buck K, Voehringer P, Ferger B. The alpha(2) adrenoceptor antagonist idazoxan alleviates L-DOPA-induced dyskinesia by reduction of striatal dopamine levels: An *in vivo* microdialysis study in 6-hydroxydopamine-lesioned rats. *J Neurochem* 2010; 112(2): 444-52. [http://dx.doi.org/10.1111/j.1471-4159.2009.06482.x] [PMID: 19895663]
- [4] Chrysostomou C, Schmitt CG. Dexmedetomidine: Sedation, analgesia and beyond. *Expert Opin Drug Metab Toxicol* 2008; 4(5): 619-27. [http://dx.doi.org/10.1517/17425255.4.5.619] [PMID: 18484919]
- [5] Zhang B, Wang G, Liu X, Wang TL, Chi P. The opioid-sparing effect of perioperative dexmedetomidine combined with oxycodone infusion during open hepatectomy: A Randomized Controlled Trial. *Front Pharmacol* 2018; 4: 940. [http://dx.doi.org/10.3389/fphar.2017.00940]
- [6] Bhagat N, Yunus M, Karim HM, Hajong R, Bhattacharyya P, Singh M. Dexmedetomidine in attenuation of haemodynamic response and dose sparing effect on opioid and anaesthetic agents in patients undergoing laparoscopic cholecystectomy- a randomized study. *J Clin Diagn Res* 2016; 10(11): UC01-5. [http://dx.doi.org/10.7860/JCDR/2016/21501.8815] [PMID: 28050479]
- [7] Zhao JN, Kong M, Qi B, Ge DJ. Comparison of the morphine-sparing effect of intraoperative dexmedetomidine with and without loading dose following general anesthesia in multiple-fracture patients: A prospective, randomized, controlled clinical trial. *Medicine (Baltimore)* 2016; 95(33): e4576. [http://dx.doi.org/10.1097/MD.0000000000004576] [PMID: 27537587]
- [8] Mantz J, Jossierand J, Hamada S. Dexmedetomidine: new insights. *Eur J Anaesthesiol* 2011; 28(1): 3-6. [http://dx.doi.org/10.1097/EJA.0b013e32833e266d] [PMID: 20881501]
- [9] Vaughns JD, Martin C, Nelson J, Nadler E, Quezado ZM. Dexmedetomidine as an adjuvant for perioperative pain management in adolescents undergoing bariatric surgery: An observational cohort study. *J Pediatr Surg* 2017; 52(11): 1787-90. [http://dx.doi.org/10.1016/j.jpedsurg.2017.04.007] [PMID: 28465076]
- [10] Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician* 2008; 11(2)(Suppl.): S105-20. [PMID: 18443635]
- [11] Egholm JW, Pedersen B, Møller AM, Adami J, Juhl CB, Tønnesen H. Perioperative alcohol cessation intervention for postoperative complications. *Cochrane Database Syst Rev* 2018; 11CD008343 [http://dx.doi.org/10.1002/14651858.CD008343.pub3] [PMID: 30408162]
- [12] Liu Y, Liang F, Liu X, Shao X, Jiang N, Gan X. Dexmedetomidine reduces perioperative opioid consumption and postoperative pain intensity in neurosurgery: A meta-analysis. *J Neurosurg Anesthesiol* 2018; 30(2): 146-55. [PMID: 28079737]
- [13] Geng J, Qian J, Cheng H, Ji F, Liu H. The influence of perioperative dexmedetomidine on patients undergoing cardiac surgery: A meta-analysis *PLoS One* 2016; 11(4): e0152829.
- [14] Singh PM, Panwar R, Borle A, Mulier JP, Sinha A, Goudra B. Perioperative analgesic profile of dexmedetomidine infusions in morbidly obese undergoing bariatric surgery: A meta-analysis and trial

- sequential analysis. *Surg Obes Relat Dis* 2017; 13(8): 1434-46.
[<http://dx.doi.org/10.1016/j.soard.2017.02.025>] [PMID: 28396128]
- [15] Schnabel A, Reichl SU, Poepping DM, Kranke P, Pogatzki-Zahn EM, Zahn PK. Efficacy and safety of intraoperative dexmedetomidine for acute postoperative pain in children: A meta-analysis of randomized controlled trials. *Paediatr Anaesth* 2013; 23(2): 170-9.
[<http://dx.doi.org/10.1111/pan.12030>] [PMID: 23043461]
- [16] Sun Q, Liu S, Wu H, *et al.* Dexmedetomidine as an adjuvant to local anesthetics in transversus abdominis plane block: A systematic review and meta-analysis. *Clin J Pain* 2018; 35(4): 375-84.
[<http://dx.doi.org/10.1097/AJP.0000000000000671>] [PMID: 30475260]
- [17] Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009; 6(7) e1000097
[<http://dx.doi.org/10.1371/journal.pmed.1000097>] [PMID: 19621072]
- [18] Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions* Version 6 [Update September 2018] The Cochrane Collaboration. <https://training.cochrane.org/handbook>
- [19] Wells GA, Shea B, O'Connell D, *et al.* http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 6 July 2019).
- [20] GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328(7454): 1490.
- [21] FDA's "Reduce the Risk" Campaign Tackles Opioid Exposure.. Available at: <https://www.fda.gov/drugs/ensuring-safe-use-medicine/safe-opioid-disposal-remove-risk-outreach-toolkit> (accessed 6 July 2019).

© 2019 Fiore *et al.*

This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International Public License (CC-BY 4.0), a copy of which is available at: (<https://creativecommons.org/licenses/by/4.0/legalcode>). This license permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.