Peer Review File

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First Round

Reviewer A

Comment 1: The publication provides interesting insight into the use of dexmedetomidine, however the authors would benefit from further descriptions of the type of treatment provided, complexity, and why the use of this sedative agent is superior to others, given that midazolam was also required to be used to maintain sedation if so how much was required. Was the fentanyl required for any of the cases? Could the treatment be provided with Midazolam alone. The paper requires significant rewriting in the discussion section, as sentences are added which do not follow the prose. The figures do not provide any significant additional information, therefore a review of if different information could be presented in a tabulated form such as outcomes, asa, total sedation, drugs % length of treatment, may be more pertinent for the reader. The author's would also benefit from discussing why this novel treatment should be used in practice compared to Midazolam or Propofol for example.

Reply 1: Thank you the reviewer for raising this point. It's still unclear which medications are best for conscious sedation during ambulatory surgical operations. An optimal anesthetic agent for conscious sedation has to alleviate a patient's stress, facilitate a swift recovery, and exhibit minimal adverse effects. Intravenous dexmedetomidine as an anesthetic adjuvant decreases opioid and anesthetic requirements in various clinical applications. Opioids are the cornerstone of pain management. However, their use is associated with a variety of adverse effects, such as respiratory depression, nausea, and vomiting. Postoperative nausea and vomiting may cause severe discomfort and delayed discharge among ambulatory patients. However, the use of a sole anesthetic agent may not be sufficient for all stages of dental surgery with a conscious sedation technique. The initial part of the procedure can be very stimulating and painful with the injection of local anesthesia.
Wang et al compered dexmedetomidine with propofol for conscious sedation. Administration of dexmedetomidine decreases the requirements of fentanyl and pain score.
The idea of the figures were to illustrate the dexmedetomidine stability during all the procedure. We also include in the review a table that summarize ASA, outcomes and monitoring of the patients.
The paper had the discussion rewrite as you kindly suggested.
Changes in the text: in highlights, we have modified our text as advised

Reviewer B

This case report describes dexmedetomidine sedation with TCI in three patients undergoing dental surgery; the three patients progressed without adverse events or prolonged hospitalization, suggesting the usefulness of dexmedetomidine sedation with TCI.

Comment 2: General Comments
The usefulness of dexmedetomidine in dental sedation has been reported in many cases, but as the authors show, bradycardia and hypotension are the main side effects. I guess that they would like to state that this side effect could be avoided by the use of TCI. However, the manuscript is not properly structured, making the claim difficult to understand.

Reply 2: Thank you the reviewer for raising this point. The relatively low dose of dexmedetomidine used in our study may explain the absence of adverse hemodynamic events.
The inconsistences between trial related to adverse events of dexmedetomidine can be explained by different dosing, additional drugs used for sedation, different comparators and types of procedures.
As a result of predictable pharmacokinetics and a rapid distribution half-life of 5–6 min after bolus injection, dexmedetomidine may be titrated to a desired effect. Prolonged infusions of dexmedetomidine, however, may lead to delayed sedative effects after discontinuation of the drug because of a longer context-sensitive half-life. The use of TCI modes may also be helpful to prevent these adverse effects and the effects arising from the pharmacological interaction of midazolam, opioid and dexmedetomidine.
Changes in the text: in highlights, we have modified our text as advised

Comment 3: Abstract
To aid reader comprehension, the manuscript should be structured as Background, Case description, and Conclusion, as indicated by the Authors Guideline. In particular, the Case description should include sufficient information.

Reply 3:Thank you the reviewer for raising this point. The abstract has been appropriately restructured.
Changes in the text: in highlights, we have modified our text as advised

Comment 4: Major comment
Main text
To help readers understand the case, the Introduction, Case Presentation, Discussion, and Conclusions should be included, as indicated in the Authors Guideline

Reply 4:Thank you the reviewer for raising this point and for allowing us to correct it as indicated in authors guidelines.
Changes in the text: in highlights, we have modified our text as advised

Comment 5: This manuscript is particularly lacking in Case Presentation; the content of Discussion (page 3, lines 138-150) should be presented in the case presentation. Figure 1 should be placed in the case presentation. Furthermore, Figure 1 shows data for three patients at the same time, but it would be better to show the anesthesia record for each patient (vital signs, oxygen, time of dexmedetomidine, midazolam, and fentanyl administration, start and end time of surgery, etc.).

Reply 5:Thank you the reviewer for raising this point. The content of Discussion (page 3, lines 138-150) was moved to the case presentation.
Changes in the text: in highlights

Comment 6: The Introduction is inadequate; the Introduction should give the reader a brief background, what is known and what is not known. It does not convey why the focus is on dexmedetomidine and why TCI is necessary.

Reply 6: Thank you the reviewer for raising this point . We have tried to focus on dexmedetomidine TCI in the introduction. Dexmedetomidine is widely used during conscious sedation, because it provides arousable sedation with less effects on respiration. The conventional infusion method is zero-order infusion which is administered as a maintenance infusion after a loading dose for 10 minutes. During the conventional infusion process, it is hard to predict the clinical effect and consequently the adverse effects. Many Dexmedetomidine pharmacokinetic models has been published since Dyck et al demonstrated the first PK model in 1993. The model of Hannivoort et al most accurately predicted the dexmedetomidine plasma concentration in patients , however, no validation has been reported in clinical trials.

We have administered a target-controlled infusion (TCI) of dexmedetomidine at the plasma- site concentration (CP) to patients undergoing dental surgery and we could observe the relationship between the dexmedetomidine CP and the sedative effects.
Changes in the text: in highlights, we have modified our text as advised

Comment 7: Minor comment
"Case series" should be changed to "case report" (page 2, line74)

Reply 7: Thank you the reviewer for raising this point. It was already corrected.
Changes in the text: in highlights

Comment 8: Reference should be added (page 3, line105)

Reply 8: Thank you the reviewer for raising this point.
Changes in the text: in highlights

Reviewer C

In this article, the authors report three cases of intravenous sedation (IVS) with dexmedetomidine (DEX) that were successfully managed using TCI for dose adjustment. I think this will be of interest to many readers. On the other hand, there are many parts of the article that are not fully explained. Therefore, I believe that some major changes are needed for publication in this journal. I hope my comments below will be helpful.

Comment 9: 1. I believe that the background and anesthetic course of each case should be described in more detail. The aim of this case series is to show the effective dose of conscious sedation for invasive dental procedures using DEX, the administration rate of which is defined by TCI. The depth of sedation of a patient varies greatly depending on the invasion as well as the blood concentration of the drug. Therefore, I believe that the dental treatment, vital signs (SpO2, blood pressure, heart rate), drug dosage (rate), expected blood concentration of DEX calculated by the TCI model used, and depth of sedation should be clearly presented over time for each case.

Reply 9: Thank the reviewer for this suggestion. In this edited version, we present a table with patient data in the intraoperative period. We believe that the description of figures 1 and 2 in the edited version may show the hemodynamic stability during the surgery. The relatively low dose of dexmedetomidine used in our study may explain the absence of adverse hemodynamic events.
Changes in the text: in highlights we have modified our text as advised

Comment 10: 2. About Figure. In this report, only systolic blood pressure and heart rate are shown. Certainly, these are indicators of the stress response to invasion (sympathetic hyperactivity), but since an important premise of this report is the success or failure of sedation, I believe it would be desirable to also describe the depth of sedation (e.g., OAA/S). I also think it would be desirable to record them at least every 5 minutes during the IVS, although they are recorded every 20 minutes (I think it would be easier to understand if they were shown together in one).

Reply 10: Thank the reviewer for this suggestion. We have tried to modified the figures to be clearer to understand.

Changes in the text: in highlights, we have modified our text as advised

Comment 11: 3. About concomitant use of midazolam (in some or all cases?). This is a serious issue to be considered in this report where the sedative effect of DEX is the subject. A full explanation needs to be added, including whether the dose and timing of midazolam administration was standardized in each case.

Reply 11: Midazolam is most frequently used for agent for conscious sedation. It has a fast onset time for sedative
effects and a fast recovery period. But the half-life of its active metabolite is long. With repeated dosages it results in prolonged sedation and a sleepy state; also, it can result in respiratory depression by decreasing respiratory response to carbon dioxide. In conclusion, dexmedetomidine provides a more efficient hemodynamic stabilization without respiratory depression. Thus, we believe that dexmedetomidine is a sedoanalgesic, which may come to be preferred and used efficiently in dental surgeries.
The use of a sole anesthetic agent may not be sufficient for all stages of a dental surgery with a conscious sedation technique. The initial part of the procedure can be very stimulating and painful with the injection of local anesthesia,. During this time the patient may require additional sedation and analgesia. Small doses of midazolam can significantly reduce the dosages of dexmedetomidine when used during the procedure. It is conceivable that this additive interaction may also reduce possible side effects associated with each drug when used alone. Moreover, it is important to note that dexmedetomidine alone does not induce amnesia, a crucial aspect of these procedures. To address this, small doses of midazolam are administered to prevent patients from remembering the procedure.

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Comment 12: 4. About concomitant use of fentanyl. Was it used in all cases? If it was used in some cases, the dosage and respiratory depression must also be fully explained. The possibility of respiratory depression cannot be completely excluded, even at low doses. In my opinion, respiratory findings during anesthesia should be described.

Reply 12: The use of a sole anesthetic agent may not be sufficient for all stages of a dental surgery with a conscious sedation technique. The initial part of the procedure can be very stimulating and painful with the injection of local anesthesia,. During this time the patient may require additional sedation and analgesia. It is important that the patient does not experience pain during this part of the procedure. Therefore, we administered an initial dose of fentanyl to all patients in our protocol.
The main safety concerns with conscious sedation in non-intubated patients are airway compromise, hypoventilation and oxygen desaturation.
According to Wang et al, administration of dexmedetomidine decreases the requirements of fentanyl and pain score.
None of the patients experienced severe bradycardia requiring atropine sulfate administration, hypotension, or discomfort during the procedure. Patient satisfaction and postoperative hospital stays showed no significant differences. In one instance, a third patient exhibited signs of upper airway obstruction but promptly responded to jaw extension and supplemental oxygen therapy. None of the patients required endotracheal intubation or mechanical ventilation.
Changes in the text: in highlights, we have modified our text as advised