Postoperative Analgesic Effect of Intravenous Dexmedetomidine in Mandibular Third Molar Extractions

A Thesis Presented in Partial Fulfillment of the Requirements for the Degree Master of Science in the Graduate School of The Ohio State University

By

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Abstract

*Purpose:* To evaluate the efficacy of intraoperative intravenous dexmedetomidine in the management of postoperative analgesia, its impact on recovery time, and surgical operating conditions in mandibular third molar extractions.

*Methods:* Nineteen healthy adult volunteers aged 18-40 years, who had already consented to the removal of bilateral mandibular third molars with local anesthesia and intravenous sedation were introduced to this study and offered the opportunity to participate in this randomized cross-over clinical investigation. Two sedation protocols were employed in the study: protocol A - the control sedation (2 mcg/kg Fentanyl followed by propofol infusion) and protocol B – the experimental sedation (1 mcg/kg dexmedetomidine infusion over 10 minutes followed by propofol infusion). The numbers 1-20 were randomly assigned to participants as they were scheduled for their first appointment. Patients received either the control or experimental protocol at their first appointment based on their randomized assignment and then received the other option at the second appointment. Following each sedation, postoperative pain scores were recorded as the patient arrived in PACU, at patient discharge, and 6 hours postoperatively. Additionally, the surgeon was asked to grade the operating conditions and level of patient cooperation experienced during the sedation. Surgical time and time in PACU until
discharge were both recorded. After the final appointment, the patient was contacted and asked to rate their sedation preference.

**Results:** Eighteen patients completed the study. Pain scores between groups were not significantly different upon the arrival to PACU, at discharge, at 6 hours postoperatively, or at the time of taking the first pain pill. However, in both groups, there was an expected difference in pain scores between both arrival and discharge from PACU to the time the first pain pill was taken. The time interval between discharge and the first pain pill was significantly different with a p-value of 0.0078. This time was about 1 hour longer in the patients following the experimental sedation (3.55 hours) than the control sedation (2.59 hours). The only other component proving to have a measurable difference was the discharge time based on the sedation protocol (p = 0.0084). Recovery time was on average four minutes longer following the experimental sedation compared to the control sedation. Surgeon’s grade of operating conditions was not significant, however showed greater variability in the grading of cases with the experimental sedation and more predictable operating conditions with the control sedation. Patient preference was not significant.

**Conclusion:** Dexmedetomine is an alpha-2 agonist with anxiolytic, sedative and analgesic properties that can be safely used in ambulatory anesthesia for dental and oral surgery procedures. Its unique properties of having no appreciable effect on respiratory drive, providing longer lasting analgesia, attenuating the sympathoadrenal response to stress, increasing the opioid-free interval, and
providing for a comfortable recovery may be beneficial in treatment of specific patients, such as patients diagnosed with obstructive sleep apnea, obesity, systemic hypertension or preexisting myocardial ischemia. More research in this area is necessary to investigate other combinations of sedative adjuncts with dexmedetomidine and its potential impact on outpatient anesthesia.
Dedication

This document is dedicated to all the past, present, and future residents of The Ohio State University Dental and Maxillofacial Anesthesiology Residency. To the past residents, thank you for paving the way for our dynamic and wonderful profession, as well as keeping research an important component of our program. To the present residents, it has been a pleasure going through this experience of residency with you and I will always keep you close to my heart as friends and colleagues. To the future residents, always be curious and open to expanding your mind; it is during these times you will find that you learn the most. Residency is demanding, but put your all into it – the results are worth it.
Acknowledgments

I would like to acknowledge all of the people that helped me tackle this project and offered their encouragement and time to help me achieve this level of professional success.

First I would like to thank my committee members.

Dr. Prior, I have learned so much from you about research and how to be an outstanding clinician. Thank you for inspiring me in my research ideas and helping through every step of the way, you have been a wonderful mentor. Later in life, when I am forever grateful I continued on this Master’s tract, I will think of you and our many afternoons spent working on IRB submission, reviewing protocols, discussing results of data analysis and figuring this all out together. Thank you for never letting me give up.

Dr. Johnston, I appreciate your dedication to my research project and all the time, emails, and face-to-face meetings we shared to make sure the data would be collected correctly and analyzed. You are truly an asset to my committee and none
of this would have been possible without your input and knowledge base and for this, I thank you.

Dr. Smiley, Thank you for always being supportive of my decision to pursue the Master’s degree through our program and discussing my project with me at length when I was able to spend some time with you at Children’s DSC. I am inspired by your positive outlook and involvement in research both with our program and the pediatric dental residency here at OSU, as well as your continue desire to promote excellence in our field.

Additionally, I would like to thank both of the surgeons who were chosen to be operators in the study.

Drs. Daniel Leach and Christy Lottinger. Without your commitment to education and the willingness to perform extra third molar consults and surgeries, this study would not have been possible. Thank you for often giving up the spare few minutes where you could have eaten lunch to help me with my project and see patients when you were also expected to perform other duties at the same time.

Last, but definitely not least, I would like to thank Adam Holowecky, the best research assistant I never knew existed before this project. You have been a
wonderful assistant and overall, a joy to work with! You have time and time again
gone above and beyond the tasks asked of you and I appreciate all your hard work!
Vita

2008 ................................................................. B.S. Biology College of Charleston
2012 ................................................................. DMD, Medical University of South Carolina
2012 ................................................................. General Practice Residency, The Ohio State University
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Fields of Study

Major Field: Dentistry (Anesthesiology)
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Introduction

Dexmedetomidine is an alpha-2 adrenergic agonist, commonly used in ICU settings to help with the sedation and comfort of patients who need to remain intubated for prolonged periods of time. This drug is also used extensively in pediatric anesthesiology as either a premedication for the uncooperative child or intraoperatively to help prevent the occurrence of emergence delirium or agitation.\(^1\)\(^-\)\(^3\) Much of the anxiolytic and sedative effects of dexmedetomidine have been evaluated in prior studies, but there has not been a great deal of research into the usefulness of the analgesic properties this drug possesses in the out-patient postoperative environment.

Alpha-2 agonists are found to have anti-inflammatory properties, possibly occurring from the production of inflammatory cytokines through their central sympatholytic action, which might play a role in reducing post-operative pain.\(^4\) The acute postoperative pain model following extraction of third molars is a very reliable, reproducible, and effective venue to test whether or not incorporating the intraoperative use of intravenous dexmedetomidine provides some benefit to postoperative analgesia in a population of healthy adults.\(^5\)\(^,\)\(^6\) Intranasal
premedication with dexmedetomidine prior to third molar extraction was used in a study at the University of Hong Kong, looking primarily at the intraoperative sedative and analgesic effects. The authors noted that patients receiving intranasal dexmedetomidine tended to have decreased postoperative pain compared to the placebo group, however, the intravenous administration of dexmedetomidine was not evaluated in their study. 4

A study in 2013 compared a common sedative combination of midazolam-fentanyl together with dexmedetomidine in monitored anesthesia care for outpatient ENT tympanoplasty procedures. 7 In this study they reported a higher patient and surgeon satisfaction score in the dexmedetomidine group, additionally significantly more patients in the midazolam-fentanyl group required rescue analgesia (fentanyl) intraoperatively than those in the dexmedetomidine group. 7 Unlike the combination of benzodiazepines and opioids, the sedative effects of dexmedetomidine are not associated with respiratory depression. This reason adds further interest in the use of intravenous dexmedetomidine rather than intravenous fentanyl in dentoalveolar surgery under monitored anesthesia care or general anesthesia, particularly so when treating obese patients or patients with known obstructive sleep apnea (OSA). In a systematic literature review of the effects of sedatives and anesthetics in patients with obstructive sleep apnea, authors report that the use of alpha-2 agonists in OSA patients perioperatively decreased opioid requirements and pain scores, contributing also to a smooth emergence from
anesthesia. If the analgesic effects of intravenous dexmedetomidine are proven adequate in the oral surgical environment then less intraoperative and postoperative narcotics may need to be administered to this patient population. The aim of this study was to compare key parameters between two types of sedation. The sedation techniques used were Propofol with Fentanyl and Propofol with Dexmedetomidine. The following parameters were compared:

- Postoperative pain
- Recovery time
- Recovery score
- Operating conditions
- Patient preference

Our Null Hypotheses were:

There was no difference between the two sedation methods with reference to postoperative pain, recovery time, operating conditions or patient preference.
Methods

After approval from The Ohio State University Human Subjects Review Committee, nineteen patients were enrolled to take part in this single-blind crossover clinical investigation. All patients were American Society of Anesthesiologists (ASA) Physical Status I or II and between the ages of 18 and 40 years. Patients with any systemic disorders, chronic pain conditions, or known allergies to medications used in the study were excluded. In addition, any patients that were ASA status III or higher, prisoners or wards of the state, minors, mentally challenged or developmentally disabled, pregnant, or nursing were also excluded from participation. Patients selected for this study were from those presenting to the Department of Oral and Maxillofacial Surgery at The Ohio State University College of Dentistry who desired intravenous conscious sedation for third molar extraction and had already given consent for the extraction of bilateral mandibular third molars under intravenous sedation. Patients who participated in this study received parking passes for each appointment at no charge and the sedation fee was waived.

To minimize the systematic error or bias in this experimental study, the subject was blinded to the anesthetic technique used for each procedure, additionally the surgeon, who provided an assessment of the surgical operating conditions, and the
researcher collecting the data were blinded to the sedation technique being evaluated during the collection of all data points in the study.

A study size of 20 patients was chosen for this introductory study to evaluate the use of dexmedetomidine during routine oral surgery. This sample size was developed by performing a power analysis based on data from similar study models comparing two different sedation techniques and evaluating differences in pain scores. There are three ways to interpret this power analysis. In all of them the "Effect size" is the ratio of the detectable mean difference of the two anesthetic regimens to (divided by) the standard deviation of the differences over all of the subjects:

1) Even using ranked data to detect an effect size of 1.0 difference in pain scores, only a subject size of 16 would be needed. This effect size was estimated assuming that a standard deviation of 1.0 and the ability to detect a mean difference in pain scores of 1.0 would be present between the two anesthesia regimens.

2) Using a quantitative continuous scale over the entire range of zero to ten, still only 16 subjects would be needed to detect an effect size of 1.0.

3) This analysis assumes it is possible to get 20 subjects, and shows that this would allow for the ability to detect an effect size of 0.85. This indicates that 20 subjects will be able to detect smaller differences in the scores than the standard deviation of the differences in these scores for all of the subjects.
The patients were presented with information regarding the research project and the appropriate IRB approved consent and HIPAA paperwork to review. Once all questions had been answered and the patients had decided to proceed with surgery, and signed the research paperwork, the research required appointments were made for surgery. The surgical procedures were limited to the surgical extractions of mandibular third molars and ipsilateral maxillary molars if present. The dentist anesthesiologist performing the sedation also administered the local anesthetic for the surgical procedures. The experimental portion of this protocol involved the use of two different sedative regimens, a different one to be used at each appointment, in order to enable a comparison of techniques and efficacy of post-operative analgesia. The anesthesiologist performing the sedation in this study, and the nurse participating in recovery, were not blinded to the sedation protocol used at either appointment, however the research data recorder, surgical operator, and the patient were blinded to the particular sedation technique being used.

The study required participants to schedule two appointments; at each appointment the patient would have the extraction of one mandibular third molar (either right or left) and the ipsilateral maxillary third molar if present. The numbers 1-20 were randomly assigned to each new participant and from this point on, all research data gathered was labeled with the randomly assigned number only. Those assigned an even number received Sedation Protocol A (control) at their first appointment and Sedation Protocol B (experiment) at their second appointment. Those assigned an
odd number received Sedation Protocol B at their first appointment and Sedation Protocol A at their second appointment. The two sedation protocols utilized were:

Protocol A (Control): patients received 2 ug/kg of fentanyl administered over 2 minutes followed by a continuous infusion of propofol beginning at 50mcg/kg/min initially and titrated to maintain a level of moderate sedation.

Protocol B (Experiment): patients received a loading dose of 1ug/kg dexmedetomidine given slowly over 10 minutes and followed by a continuous infusion of propofol beginning at 50mcg/kg/min and titrated to maintain a level of moderate sedation.

Additional boluses of propofol were given in 20 mg increments if required in either protocol, and this information was recorded on the anesthetic record.

Upon arriving to the clinic, and prior to initiation of sedation, the required 8-hour fasting period was confirmed for all patients. Additionally, female patients were asked about the possibility of pregnancy and offered a urine pregnancy test for evaluation of HCG levels if they were unsure of their pregnancy status. Any patients with positive urine HCG tests were excluded from the study. Reliable phone numbers were obtained from both the patient and patient’s escort in order to be able to contact the patient 6 hours post-operatively to evaluate pain scores. Baseline
vitals consisting of blood pressure, heart rate, and oxygen saturation were obtained prior to intravenous catheter placement and monitored throughout the sedation and recovery period. Intravenous access was established in an upper extremity vein with a 20 or 22-gauge in-dwelling catheter. Once IV access had been obtained the catheter was connected to a primed line and 500ml bag of 0.9% normal saline. An ETCO$_2$ (end-tidal carbon dioxide) sampling Nasal Cannula was placed on the patient with a constant 2 liter per minute (lpm) supplemental oxygen flow given during the sedation. At this time either sedation protocol was initiated as described above. After the initial 10 minutes of sedation, allowing for completion of the dexmedetomidine loading dose required in protocol B, the dentist anesthesiologist administered 2% Lidocaine (1:100,000 epinephrine) intraorally as local anesthetic for the procedure. A propofol infusion was titrated as needed to achieve a level of moderate sedation and thereafter supplemented by repeated 20 mg boluses as needed.

After the local anesthetic had been administered, the dental assistant would bring the surgical operator into the operating suite to perform the surgery. Additional local anesthetic was administered if needed and the total amount used was recorded. The duration of surgery was recorded, beginning when the surgeon entered the procedure until completion of treatment or placement of the final suture by the surgeon. Directly following the procedure, the surgeon left the
operating suite and was asked to grade the operating conditions of the sedation based on patient cooperation and patient movement during the surgery (Table 1).

<table>
<thead>
<tr>
<th>Good</th>
<th>Patient is cooperative, operating conditions are good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
<td>Patient cooperation is obtained only with constant reminders</td>
</tr>
<tr>
<td>Poor</td>
<td>Patient cooperation is intermittent, even with constant reminders</td>
</tr>
<tr>
<td>Very Poor</td>
<td>Operation is impossible due to lack of patient cooperation</td>
</tr>
</tbody>
</table>

Table 1 – Grading Scheme of Operating Conditions

Following surgery, the patient was taken to recovery and monitored by the clinic nurse until ready to be discharged to the care of a responsible escort. After entering recovery and following a standard report to the nurse by the dentist anesthesiologist, the data collector obtained the patient’s pain score using the Wong-Baker FACES pain scale (measuring from 0-10).

Figure 1 – Wong-Baker FACES pain scale
After the patient had recovered sufficiently to achieve an Aldrete Score of 9 or 10 they were deemed ready to be discharged from the recovery facility. At this point the data collector obtained a second pain score from the patient.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to move four extremities voluntarily on command</td>
<td>2</td>
</tr>
<tr>
<td>Able to move two extremities voluntarily on command</td>
<td>1</td>
</tr>
<tr>
<td>Able to move no extremities voluntarily on command</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiration</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to breathe deeply and cough freely</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea or limited breathing</td>
<td>1</td>
</tr>
<tr>
<td>Apneic</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O2 Saturation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintains baseline saturation on room air</td>
<td>2</td>
</tr>
<tr>
<td>Needs O2 to maintain &gt;90% saturation</td>
<td>1</td>
</tr>
<tr>
<td>O2 saturation&lt;90% with O2 supplement</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Circulation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP ± 20% of pre-anesthetic level</td>
<td>2</td>
</tr>
<tr>
<td>BP ± 20 – 49% of pre-anesthetic level</td>
<td>1</td>
</tr>
<tr>
<td>BP ± 50% of pre-anesthetic level</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consciousness</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully Awake</td>
<td>2</td>
</tr>
<tr>
<td>Arousable on calling</td>
<td>1</td>
</tr>
<tr>
<td>Not responding</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2 - Modified Aldrete Scoring System

Patients were discharged with pain prescriptions for Norco 5/325mg and Ibuprofen 600mg tablets, and instructed to take them as needed following surgery. A copy of the Wong-Baker FACES pain scale (figure 1) was given to the patient to take home and use as a reference when the data collector called them 6 hours post-operatively.
to record their pain score. They were also asked to record the time at which they took the first pain medication and their pain level at that time. Following completion of both appointments patients were either seen in the clinic for a follow-up appointment or contacted by telephone and asked their preference for either the sedation they received at their first, their second appointment, or neither. Patients were encouraged to comment freely on their reasoning for any sedation or appointment preference and their comments were recorded.

The pain scores at four different time intervals (arrival to PACU, discharge from PACU, and 6 hours following procedure) were the dependent variable, treated as continuous data and analyzed for normality. If they followed a normal distribution they were summarized with means, standard deviations and 95% confidence intervals. If non-normal, the data were summarized with medians and inter-quartile ranges. The pain scores were interpretively analyzed using a repeated measures analysis of variance with maximum likelihood estimations to account for any lack of normality and Satterthwaite corrections to account for any lack of heteroscedasticity. This analysis was executed using SAS®Proprietary Software 9.3 (SAS Institute Inc., Cary, NC, USA) MIXED procedure.

For the analyses of each of Recovery Time (minutes), Time from Discharge until First Pain Pill Taken (hr), and Surgical Time (minutes), the dependent variable was analyzed by a repeated measures ANOVA using the maximum likelihood estimation
method and the Satterthwaite degrees of freedom method.\textsuperscript{10,11}

For each analysis, the factors analyzed were the "Drug Given at First Appointment", the Drug for which the Pain Score was determined, and the Time at which the Pain Score was determined. For this analysis, the interaction between Drug and Time was included. For any statistically significant factor that had more than one degree of freedom, pairwise testing of significant difference were performed.

For the analysis of the ranked categories of Operating Grades, a Mantel-Haenszel/Exact Test was used, and this analysis was executed using SAS\textsuperscript{®}Proprietary Software 9.3 (SAS Institute Inc., Cary, NC, USA) FREQ procedure. The raw data was summarized by frequencies and relative frequencies within each drug. For the categories of Preference, the raw data was summarized by frequencies and relative frequencies. For the analysis of the Preferences, an exact test for equal proportions was executed using SAS\textsuperscript{®}Proprietary Software 9.3 (SAS Institute Inc., Cary, NC, USA) FREQ procedure. A probability (p) value $<0.05$ for any parameter test was considered statistically significant.
Results

Nineteen patients completed this crossover study. The study population consisted of 8 males and 11 females, with an age range of 18-33 years and a mean age of 23.2 years. Patient weight was recorded in kilograms and ranged between 43-100kg with a mean weight of 71kg. Procedures performed in each surgical appointment were uniformly the extraction of ipsilateral third molars, either the right side or left side, with the exception of one patient who also required, on one side, the extraction of the root tips of an adjacent molar. The surgical nature and extent were therefore similar in nature for all operative events.

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.16 ± 5.12</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>8/11</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 15.99</td>
</tr>
<tr>
<td>Surgery Duration (minutes)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>10.96 ± 8.22</td>
</tr>
<tr>
<td>Experiment</td>
<td>10.02 ± 6.85</td>
</tr>
<tr>
<td>Recovery Duration (minutes)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>15.32 ± 4.24</td>
</tr>
<tr>
<td>Experiment</td>
<td>19.22 ± 6.16</td>
</tr>
</tbody>
</table>

Table 3 – Patient Characteristics
Pain scores were measured at four different times postoperatively, upon arrival to PACU where the FACES pain score averaged 0.21 (experiment) to 0.61 (control), at discharge from recovery with a score of 0.71 (experiment) to 0.76 (control), at 6 hours following discharge where the pain was rated with a mean of 1.95 (control) to 2.24 (experiment), and finally at the time the first pain pill was taken, if this was within the 6 hour observation period; 6.38 (control) and 7.00 (experiment) (Table 2). These results were evaluated via a repeated measures analysis and the mean pain scores are listed below in table 4 and displayed in figure 2. The results showed no significant differences in pain scores at the various observation times that could be attributed to the different sedation protocols being used, however there were differences in pain scores for the different times of pain assessment. As to be expected, pain scores at arrival to PACU and discharge from recovery were significantly different from the pain scores measured prior to the time of taking the first pain pill or 6 hours postoperatively. Just as one would see following most surgical procedures under sedation, there was an increase in discomfort between leaving the PACU with a pain score on average between 0.71-0.76 and the patient taking the first analgesic tablet with a pain score at the time of postoperative analgesic administration of 6.38 following control sedation and 7.00 following the experimental sedation.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Time</th>
<th>Mean Pain Score</th>
<th>StdDev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>PACU</td>
<td>0.61</td>
<td>1.67</td>
</tr>
<tr>
<td>Control</td>
<td>Discharge</td>
<td>0.76</td>
<td>1.32</td>
</tr>
<tr>
<td>Control</td>
<td>6 hours</td>
<td>1.95</td>
<td>1.40</td>
</tr>
<tr>
<td>Control</td>
<td>1st Analgesic</td>
<td>6.38</td>
<td>2.09</td>
</tr>
<tr>
<td>Experiment</td>
<td>PACU</td>
<td>0.21</td>
<td>0.54</td>
</tr>
<tr>
<td>Experiment</td>
<td>Discharge</td>
<td>0.71</td>
<td>0.93</td>
</tr>
<tr>
<td>Experiment</td>
<td>6 hours</td>
<td>2.24</td>
<td>1.36</td>
</tr>
<tr>
<td>Experiment</td>
<td>1st Analgesic</td>
<td>7.00</td>
<td>2.31</td>
</tr>
</tbody>
</table>

Table 4 - Mean Pain Score Postoperatively

In the final data analysis, the pain scores of only 19 subjects were included in the analysis. Additionally, the “Time from Discharge until First Pain Pill Taken (hr)” and the “Pain score prior to taking 1st pain pill” of subjects who never took a pain pill was treated as missing data. Two patients did not take pain medication following either sedation within the first 6 hours postoperatively. One other patient did not take a pain medication just following the control sedation and another patient did not take a pain medication just following the experimental sedation.
The only statistically significant differences seen between the control and experimental groups were the time spent in recovery until discharge (Table 6) and the time from discharging the patient until an analgesic medication was taken postoperatively (Table 7).

The recovery time was slightly longer following the experimental sedation than the control sedation, a difference however of approximately 4 minutes only (Figure 3 and Table 5). In Table 6, this is noted for significance with a p value = 0.0081.

Interestingly the experimental group experienced a greater variability in recovery
from the sedative procedure than the control group, displayed by the standard deviations and upper and lower confidence levels in Table 5.

![Figure 3 - Recovery Time](image)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean (minutes)</th>
<th>Standard Deviation (minutes)</th>
<th>Lower 95% Confidence Level Limit</th>
<th>Upper 95% Confidence Level Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>15.32</td>
<td>4.24</td>
<td>13.27</td>
<td>17.36</td>
</tr>
<tr>
<td>Experiment</td>
<td>19.05</td>
<td>6.03</td>
<td>16.15</td>
<td>21.96</td>
</tr>
</tbody>
</table>

Table 5 - Mean Recovery Time

<table>
<thead>
<tr>
<th>Effect</th>
<th>FValue</th>
<th>ProbF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug 1st Appointment</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td>Drug</td>
<td>8.74</td>
<td>0.01</td>
</tr>
<tr>
<td>Drug 1st App*Drug</td>
<td>1.38</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Table 6 - Mean Recovery Time - Statistical Evaluation

The first oral pain medication was taken on average 2.59 hours after discharge in the control group and 3.55 hours after discharge by patients receiving the experimental sedation respectively (Figure 4). This difference was statistically
significant with a P value = 0.0078, displayed in Table 8 below.

![Bar chart comparing control and experiment groups for time to first oral analgesic](chart.png)

Figure 4 - Time to First Oral Analgesic

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time to First Oral Analgesic (Hours)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2.59</td>
<td>1.12</td>
</tr>
<tr>
<td>Experiment</td>
<td>3.55</td>
<td>1.25</td>
</tr>
</tbody>
</table>

Table 7 - Time to First Oral Analgesic

<table>
<thead>
<tr>
<th>Effect</th>
<th>F – Value</th>
<th>Probability F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug 1st Appointment</td>
<td>0.07</td>
<td>0.79</td>
</tr>
<tr>
<td>Drug</td>
<td>9.19</td>
<td>0.01</td>
</tr>
<tr>
<td>Drug 1st Appointment*Drug</td>
<td>0.77</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Table 8 - Time to First Oral Analgesic - Statistical Evaluation

The surgeons’ grading of the operating conditions was not significantly different between the sedation protocols being investigated in this study. In the control group, a greater number of the sedations received a “good” rating, 15 of 19, whereas
in the experimental sedation group only 11 of 19 received a “good” rating. In the control group there were 2 sedations that received a “fair” rating, in comparison to 4 sedations in the experimental group. Four sedations from the experimental group were rated as poor or very poor, where only 2 of the sedations in the control group received a rating of poor or very poor (Table 9).

<table>
<thead>
<tr>
<th>Operating Grade</th>
<th>Control</th>
<th>Experiment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>15</td>
<td>11</td>
<td>26</td>
</tr>
<tr>
<td>Fair</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Poor</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Very Poor</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>19</td>
<td>38</td>
</tr>
</tbody>
</table>

Table 9 - Rank of Operating Conditions by Surgeon

The patient preference was the final factor assessed at about 1-2 weeks following completion of both surgical appointments and the use of both sedation protocols. The results from this data showed that half of the patients preferred the experimental sedation (50%) and slightly less than half preferred the control sedation (44%), with one patient having no preference at all (6%).
Surgery time was similar at both appointments either and not influenced by which drug was given at the first appointment or the specific drug itself (Table 10).

<table>
<thead>
<tr>
<th>Effect</th>
<th>F Value</th>
<th>Prob&gt;F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug at 1st Appointment</td>
<td>0.49</td>
<td>0.49</td>
</tr>
<tr>
<td>Drug</td>
<td>0.26</td>
<td>0.62</td>
</tr>
<tr>
<td>Drug * at 1st Appointment*Drug</td>
<td>0.12</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Table 10 - Surgery Duration
Discussion

There are a multitude of scientific investigations regarding the use of dexmedetomidine as an anesthetic adjunct in both adult and pediatric cases. The majority of this literature deals with associated changes in hemodynamic stability, effects on emergence delirium, or the sedative, anxiolytic properties of dexmedetomidine, rather than specifically looking at the analgesic properties of this drug and their effect on recovery. In this crossover study, the aim was to evaluate the postoperative analgesic effects of intravenous dexmedetomidine and to compare them to those seen with the use of intravenous fentanyl, an opioid commonly used in outpatient surgery. Dexmedetomidine is significant in the fact that it does not cause an appreciable amount of respiratory depression and this could be an important focus in the treatment of patients with preexisting pulmonary conditions, obstructive sleep apnea, or obesity.

Dexmedetomidine is a highly selective alpha-2 agonist, similar to clonidine, however dexmedetomidine has a much greater affinity for the alpha-2 receptor (8 times the affinity of clonidine for the receptor). These receptors work primarily in the sympathetic nervous system, and when activated initiate a negative feedback loop
modulating the release of norepinephrine. This mechanism allows for the attenuation of the sympathetic stress response, which is an important function of these drugs in surgical patients, especially patients with preexisting cardiac conditions, such as systemic hypertension or myocardial ischemia. 13-15 Additionally, alpha-2 receptors are found in the locus ceruleus and spinal column – it is these locations that promote the properties of sedation, anxiolysis, and analgesia. The locus ceruleus is the predominant noradrenergic nucleus in the brain and serves as a modulator of wakefulness and vigilance. 16 In the spinal column, activation of these receptors inhibits nociceptive neurons, and in turn, decreases the production of substance P. 14 These properties, combined with the lack of respiratory depression associated with dexmedetomidine, make it a great adjunct for providing sedation for surgery in an ambulatory setting. The author designed this crossover study to specifically compare these properties and analgesic effects with those of fentanyl, a commonly used opioid in mandibular third molar extractions.

Overall, the results showed that the pain scores were similar upon arrival to the PACU and at discharge from PACU. This is to be expected with the duration of local anesthetic activity extending well beyond the typical PACU duration. However at 6 hours postoperatively the pain scores varied greatly. This is possibly best appreciated simply as a result of the variation in the time period between leaving the treating facility and the patients deciding to begin their home oral analgesics. As
a consequence it was thought that the better area to focus on when attempting to
gain an insight into the efficacy of one sedation technique over another was whether
or not the intravenous sedation medications had a longer-lasting effect on pain
relief in the number of hours following discharge from PACU until the patient
decided pain medication was necessary. We found there was a significantly greater
time until pain medicines where taken when propofol and dexmedetomidine were
the sedatives used rather than following a propofol and fentanyl procedural
sedation. This was also a factor noted in previous research using the
dexmedetomidine for outpatient gynecologic procedures, postoperative
management of scoliosis surgery, and children requiring tonsillectomies. All these
studies show patients had less postoperative analgesia and an increased opioid-free
interval following procedures. 2,17-19 This finding would suggest that
dexmedetomidine may be a better combination for patients where a longer duration
between operation and home care may be anticipated (e.g. patients travelling a long
distance between procedural location and home) or as an adjunct in the sedation of
patients with OSA or obesity where it would be desirable to avoid the added
hypoventilation that may be anticipated with the use of narcotics. In a previous
study, after receiving dexmedetomidine intraoperatively during routine
tonsillectomies, children diagnosed with OSA awakened to a smoother
postoperative course and experienced fewer episodes of desaturation than children
receiving opioids intraoperatively. 2 The analgesic benefits seen here in the oral
surgery field may make this medication a viable and valuable sedative selection in
those cases where a practitioner may simply wish to reduce or avoid altogether intraoperative and postoperative narcotics. Another factor that may have influenced the results became apparent as the data recorder gathered information from the patients. The discharging nurses may not have given completely uniform instructions regarding the taking of the first pain medication, some patients may have understood that the first pain medication was to be taken before the local anesthetic dissipated, as is usually the institutional practice, and not to wait until they found it clinically necessary, the latter was the original design of the study.

A difference in recovery time was also noted to be significant, as those patients receiving dexmedetomidine in combination with propofol generally exhibited a longer recovery time than those receiving fentanyl and propofol. The time difference of four minutes, although statistically significant, was not however a difference that would be of great clinical importance in an average private practice setting. This was also depicted in a previous study comparing dexmedetomidine and fentanyl in outpatient maxillofacial procedures, where the recovery time for the dexmedetomidine group was significantly prolonged compared to the fentanyl group, in some cases the recovery time was twice as long as the procedure. It is interesting to note in the current study that the discharge time was also more variable in the experimental group, having a range of 16.15 to 22.28 minutes, whereas a fentanyl and propofol combination not only showed a quicker wake up but a more predictable recovery profile. Other studies have reported the opposite,
saying that dexmedetomidine allowed for a quicker recovery of patients due to fewer side effects, such as PONV or episodes of desaturation. In our results, it is noted that the surgical time is not influenced by either which drug is given or which drug is administered at the 1st appointment. This is important to note because it is desirable to have similar surgical situations for both appointments in a crossover study to accurately compare the sedation drugs utilized. This observation is not only interesting, but strengthens the interpretation of the statistical difference seen in our study between the control and experimental sedations.

The more unpredictable experimental sedation made judging termination of the sedation a little more challenging and although every effort was made to regulate the propofol infusion in both groups similarly, and to provide the fastest transition between satisfactory operating conditions and awakening, more of the dexmedetomidine sedations found patients still very sleepy at the conclusion of their treatment while interestingly a number of the same sedation group saw the patient more easily arousable and responding very rapidly to the lightest attempt by the anesthesiologist to awaken them by opening their eyes immediately after surgery was over and following directions. The unpredictability of dexmedetomidine in sedation has been observed in previous studies involving dental or oral surgery procedures. One study revealed that the sudden arousal to stimulation, especially sound, may be a disadvantage of dexmedetomidine’s use in dental applications where handpieces and drills are often used. One patient woke
up from the experimental sedation and proceeded to place his hands out like he was holding on to a steering wheel and driving a car, asking for directions and looking for the driveway at his house. This is interesting because he appeared to be in a dream-like state even though his eyes were open. The literature mentions this and has explained it as the result of the action of dexmedetomidine on the locus ceruleus and its ability to induce a natural physiologic sleep pattern. Additionally, a few other patients receiving the experimental sedation were seemingly disturbed by the operative procedure itself and some appeared to be quite agitated by the stimulation or pressure from the dental extractions, even possibly the sound of the drill; it appeared as if they were comfortably in a deep sleep and suddenly disrupted by an annoying stimulus. In most instances, even though these patients appeared agitated and made some movements that did not appear purposeful, they rarely ever opened their eyes which could leave one to believe they continued to stay in the dream-like state while expressing aversion towards the unpleasant stimulus. In a small number of cases this was disruptive to the surgery and may account for the lower rating of operating conditions given by the surgeon for this group. Additionally, two patients receiving the control sedation became very talkative and required multiple extra boluses of propofol (20 mg per bolus) and frequent reminders to be cooperative before the surgeon was able to continue with surgery.

Even though overall there was no significant difference in patient preference based on the specific sedation protocol utilized, there were variable results. Some patients
preferred to be more alert and awake during surgery and other patients preferred
to be completely unaware and appreciated being more drowsy. Most patients
declared they were unable to recall the events of the surgery, even when their
sedation preference was because they felt more “awake.” Two patients reported that
they felt much less pain following the dexmedetomidine sedation, however they
preferred the control sedation for other reasons. No patients reported really strong
feelings either for or against either sedation and the majority reported they would
have either sedation again. Postoperative nausea and vomiting occurred in one
patient after the control sedation and in no patients following the experimental
sedation. This patient later reported a preference for the experimental sedation,
giving the fewer side effects she experienced as the reason for her preference. In a
previous study looking at utilizing dexmedetomidine as the sole anesthetic in office-
based oral and maxillofacial surgery procedures, the authors compared a patient
group receiving fentanyl to a patient group receiving dexmedetomidine and
reported the fentanyl group experienced a significantly higher amount of
postoperative nausea and vomiting than the dexmedetomidine group. 20

In summary, dexmedetomidine is an alpha-2 agonist with anxiolytic, sedative and
analgesic properties that can be safely used for ambulatory anesthesia for dental on
respiratory drive, providing longer lasting analgesia, attenuating the
sympathoadrenal response to stress, increasing the opioid-free interval, and
providing for a comfortable recovery may be particularly beneficial in the treatment
of specific patient groups, such as patients diagnosed with obstructive sleep apnea, obesity, systemic hypertension or preexisting myocardial ischemia. Whether or not the benefit of improved post-operative analgesia observed in the test group warrants the greater expense incurred using this medication needs to be more closely assessed. It should also be noted that the suggested loading dose range for the administration of dexmedetomidine is 1-2 ug/kg and we used the lower dose. It would be valuable to repeat this study using the upper limit of the recommended loading dose and comparing outcomes. More research in this area is also necessary to investigate other combinations of sedative adjuncts with dexmedetomidine and its potential impact on outpatient anesthesia.
Conclusion

This single blind crossover study served to evaluate the efficacy of intraoperative intravenous dexmedetomidine in the management of postoperative analgesia, its impact on recovery time, and surgical operating conditions in mandibular third molar extraction. Eighteen ASA I or II patients between the ages 18 and 40 years of age underwent the two different sedation protocols (control and experiment) to complete this study. The only significant differences noted between the sedation groups were seen in recovery time measured in minutes and time from discharge until the first pain pill was taken. On average, patients receiving the experimental sedation were in recovery for a slightly longer duration (4 minutes) than patients receiving the control sedation. The time until the patient felt it necessary to take a pain pill following discharge was approximately an hour longer following the experimental sedation in comparison with the control sedation. Surgeon grading of operating conditions and patient preference did not reveal great disparity between the sedations groups. The data collected in this small crossover study with just 18 participants displays that sedation with dexmedetomidine and propofol can be safely performed for third molar extractions in an outpatient setting, providing longer analgesia than sedation with fentanyl and propofol. Additional crossover studies with similar principles in testing the usefulness of intravenous
dexmedetomidine and possibly including other adjuncts to anesthesia, could expand upon these ideas in a larger population.
References


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