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Comparative Evaluation Between Dexmedetomidine and Midazolam as Intravenous Conscious Sedative Agents Used in Minor Oral Surgical Procedures

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1. Abstract

1.1. Background and objective: Oral and maxillofacial surgery encompasses a wide spectrum of conditions affecting the oral cavity and associated structures. A lot of our work is done in the minor operative set-ups and mostly under local anesthesia. Dealing with conscious patients undergoing surgical procedures on a daily basis is an acquired skill of an astute clinician. The management of fearful and anxious patients has always been a challenge.

Many methods have been in practice to alleviate pain and relieve anxiety during surgery. Clinicians can induce a state of altered consciousness in patients so that they are more relaxed and compliant to undergo surgery. This can be achieved by behavioral modifications and non-pharmacological and pharmacological methods.

Conscious sedation is a pharmacological method of attaining a minimally depressed level of consciousness, thus blunting the awareness. Many drugs have been used for this purpose, and the present study compares the efficacy and safety of 2 drugs namely dexmedetomidine and midazolam.

The aim of the study was to compare dexmedetomidine versus midazolam. The objectives of this study were to evaluate the efficacy and safety of these two drugs as IV sedative agents for minor oral surgical procedures and also to assess the advantages and potential complications of these agents.

1.2. Methodology: The study included 20 subjects divided into 2 groups. Group I received midazolam and group II received dexmedetomidine as the IV sedative drug. The depth of sedation was measured by Ramsay sedation score and a score of 3 was set as a target. The efficacy of the drug was measured by a visual analogue scale and motor activity assessment scale. VAS was a self-rating scale where the patients would quantify their level of comfort and the MAAS was a clinician-rated scale. Both were measured at 4 events during the study which were IV cannulation, administration of local anesthetic, incision, and suturing. The safety of the drugs was measured by their ability to maintain the baseline vital signs like heart rate, blood pressure, respiratory rate, and arterial oxygen saturation while achieving the desired level of sedation efficiently.

1. 3. Results: The study results showed both the drugs were efficient and safe to be used as IV agents for inducing conscious sedation during minor oral surgical procedures.

1.4. Conclusions: The study concluded that dexmedetomidine produces similar and more reliable sedation as compared to midazolam. Although there is a decrease in heart rate and blood pressure after the use of dexmedetomidine, it is not significant and does not require corrective intervention when used in recommended doses. The decreased heart rate and blood pressure can rather be of benefit during the surgery. It does take longer recovery as compared to midazolam in a few cases.

Midazolam produces good sedation with minimal movement of the patient during surgery as compared to dexmedetomidine which causes arousal of the patient over mild to moderate auditory and tactile stimulations. It may be so, as it produces sleep-like sedation, and any stimulus can arouse the patient easily. Midazolam does cause episodes of desaturations and apnoea though not si-

gnificant to interrupt the surgery they are a concern and more vigilance is required during monitoring. Thus, both the drugs are safe and efficient and can be chosen depending on the need of the surgeon, surgery, and the patient.

2. Introduction

Maxillo-facial surgery has come a long way since its introduction as a separate surgical specialty. Though there is a drastic improvement in surgical procedures and outcomes, patients are still not comfortable visiting the doctor unless the condition becomes unbearable in some cases.

Pain is a major factor that brings patients to the healthcare provider, while the fear and anxiety about pain are common reasons patients fail to seek the required treatment and care [1]. Oral and maxillo-facial surgery is a specialty with a history of performing painful procedures. The fear of instruments, equipment, operative settings, and any other paraphernalia that may unduly increase the anxiety level of the patients who are usually in a painful crisis already, makes the situation only worse for both the patient and the surgeon. Fear of pain is a major deterrent to the delivery of the treatment in our specialty [1].

Pain and its management have always been a concern for surgeons. Pain, fear, and anxiety in our specialty are significant factors that need to be alleviated to carry out our procedures comfortably. This in some patients cannot be achieved with loco-regional anesthesia alone. A combination of sedation and local anesthesia is often employed during surgical procedures to manage these patients.

Sedation is a technique of inducing a state of altered consciousness in which the patient can be more relaxed and compliant to undergo the procedure. This method of behavioral modification can be carried out safely with predictable outcomes. Conscious sedation is an effective method of reducing patients' fear and anxiety while keeping them conscious through the procedure.

2.1. Conscious Sedation

A minimally depressed level of consciousness that retains the patient's ability to independently and continuously maintain an airway and respond appropriately to physical stimulation and verbal command and that is produced by a pharmacological or non-pharmacological method or combination thereof [3].

Sedation may be achieved with drugs given by any route of drug administration. The most preferred routes are through mouth, inhalation, or intravenous injection. Intravenous sedation is of rapid onset and the required dose is usually readily titrated against the patient's needs. The level of sedation achievable whilst maintaining patient cooperation with verbal contact is deeper than with other forms of sedation. The intravenous technique has attained the greatest popularity due to the ability to titrate the dose of sedative drug according to the response of the patient and quick onset of action [4].

Many drugs have been tried and tested for the purpose of intravenous sedation which includes benzodiazepines like Midazolam, diazepam, Lorazepam, barbiturates like phenobarbital, opioids like morphine, and fentanyl, dissociative agents like Ketamine, and many others including Clonidine, Propofol, etc. All in appropriate dose and under good supervision have produced good reproducible results.

Midazolam is a fairy known drug used for procedural sedation. It is a water-soluble imidazole-benzodiazepine with a short onset of action with plasma elimination half time of 1.5 to 2.5 hours. It is a sedative drug with amnesic properties where-in it produces anterograde amnesia. It has been widely tried, tested, and used up to date in the field of conscious sedation.

Dexmedetomidine is a selective alpha-2 receptor agonist that has been demonstrated to have sedative, analgesic, and anxiolytic effects when administered intravenously. This drug was initially recognized as an effective sedative in the intensive care unit for intubated patients. Since then, its clinical application has expanded to include neurosurgery, pediatric procedural sedation, awake fiber-optic intubation, cardiac surgery, bariatric surgery, and dental and oral and maxillofacial surgical procedures. Dexmedetomidine has sedative actions that resemble physiologic sleep, and respiratory depression is less marked. This differs from the features of benzodiazepines and propofol used in psychosedation which causes marked respiratory depression [5]. Unlike opioids, benzodiazepines, and propofol, Dexmedetomidine has been shown not to depress respiration. Its use as a single agent intravenous sedative during surgical procedures has been reported in few studies.

However, conscious sedation methods do involve some level of risk for the patient. This risk is higher than in patients being treated by local anesthesia alone, but considerably less when compared to those undergoing general anesthesia. The most important consideration when dealing with a potential emergency while performing sedation is to have a well-qualified and trained team, necessary drugs and equipment and strict guidelines. These will enable us to handle uneventful circumstances that may arise.

'The aim of the present study is to evaluate the efficacy of Dexmedetomidine versus Midazolam as IV sedative agent for minor oral surgical procedures and also assess the advantages and potential complications while using these drugs for IV sedation in minor surgical procedures.

3. Methodology

A prospective comparative randomized double-blind study was designed to compare and evaluate dexmedetomidine and midazolam as single-agent intravenous conscious sedative agents used in minor oral surgical procedures which would not exceed 90 minutes. The study started after obtaining the institutional ethics committee approval.

The subjects included were the patients who visited the Department of oral and maxillofacial surgery at A J Institute of the dental

sciences, Mangalore between December 2016 and October 2018. All the subjects were between 18 to 60 years of age and were classified as ASA 1 or ASA II according to the ASA physical status classification system [6]. ASA I patients did not require any additional investigations for evaluation of systemic conditions other than those needed for surgical workup, preceded by a thorough history, physical examination, and a medical questionnaire specially designed for patients undergoing IV conscious sedation. ASA II patients required investigations specific to their systemic illness along with regular work-up as for ASA I patients. These included tests such as blood glycemic levels, HbA1c, FBS, thyroid function test, liver function test, kidney function test, baseline ECG and echocardiogram where required, spirometry test in case of COPD patients, etc. These patients were investigated systemically as required and were included in the study after obtaining the medical fitness to undergo the planned surgical procedure under local anesthesia and conscious sedation.

This study included 20 patients who were divided into two groups. Group I received midazolam and group II received dexmedetomidine as the IV agent for conscious sedation. The patients included were scheduled to undergo a minor oral surgical procedure which would not be expected to exceed 90 minutes and would be carried out under local anesthesia supplemented by conscious sedation.

Patients with diagnosed psychiatric conditions, patients with substance abuse with recreational drugs, immunosuppressive states, drug allergy, hypersensitivity to drugs used in the study like benzodiazepines, dexmedetomidine, local anesthetics, morbidly obese patients with a body mass index of over 35 kg/m², patients with predicted difficulty for bag and mask ventilation were all excluded from the study. Patients who were on benzodiazepines, narcoleptics, and anti-epileptic drugs for more than three months were also not considered for the study.

Once the patient met the inclusion criteria, an initial pre-sedation assessment was carried out which included a general case history, descriptive data like height, weight, ASA status, a medical questionnaire with a fully recorded medical history, dental history, conscious sedation, and general anesthetic history with the diagnosis and surgical treatment plan. Hamilton Anxiety Rating Scale (HAM-A) was used to measure the severity, degree of anxiety, and symptoms in the individual patients.

The patients were prepared for general anesthesia. They were kept NPO for 4 hours prior to the surgery. Baseline parameters which included heart rate, blood pressure, arterial oxygen saturation, and respiratory rate were recorded. A strait trait anxiety index was used 1 hour before the start of the procedure to assess the anxious state of the patient.

The patient was then allocated to one group randomly using the 'Toss-a-coin' randomization technique. One of the invigilators of the study who was not directly involved in patient management and care was selected to spin the coin. If the coin showed heads, the patient was allocated to Group I and on showing tails, the patient was allocated to group II. Since the researcher did not have control over the allocation of the patient to a particular group, the study was carried on until the desired sample size was achieved.

Patients were involved voluntarily after a thorough explanation of the entailed study in the language they understood. An information sheet regarding the study was shared with all the patients. Written informed consent was taken duly signed by the patient and by the patient party caring for him. The patient caregiver also was explained the study. A written instruction about post-operative care and contact information in case of emergency was also shared. At this point, patients who did not understand VAS and its interpretation were excluded from the study.

Once the patient was allocated to a particular group, they were transferred to a minor OT/major OT, where the procedure would be performed. IV cannulation was done and secured in one of the forearms using a 20G cannula.

Patients in Group I were given 1mg Midazolam diluted in 1cc NS as a bolus dose and waited for 10min for induction of sedation. Patients in group II were given 1mcg/kg/hr as an Induction dose for 10min an infusion.

After 10mins, local anesthesia with 2% lidaciane in 1:80000 epinephrine was administered as preferred by the surgeon. Ramsay sedation scale was used intra-operatively to assess the depth of sedation, and a score of 3 was fixed as adequate sedation and a dose of IV sedative was titrated to achieve this within the limit of the maximum dose set for this study.

For group I, 1mg midazolam diluted in 1cc NS was administered every 20 minutes after the dministration of local anesthesia until the desired depth of sedation was achieved. 5mg midazolam was set as a maximum dose for the study, which would be administered by the end of 80 minutes. In both, the groups, the administration of IV sedative drug was decided to be stopped 10 minutes before the end of the procedure, if the procedure took 90 minutes to complete, or at the beginning of the suturing if the procedure would have finished early.

In group II patients, the maintenance dose was given at the rate of 0.1 – 0.7 mcg/kg which was titrated against the desired depth of sedation. Propofol was used as a rescue drug in cases of failed sedation.

Vital signs were monitored throughout the procedure using a multi-parameter heart monitor. The heart rate, blood pressure, respiratory rate, and arterial oxygen saturation were recorded every 2min during the induction phase i.e. 10min immediately after administration of the IV sedative and every 10mins during the maintenance phase.

Oxygen saturation of 92% was fixed as the lower limit after which

the procedure would be stopped, the administration of IV sedative would be ceased and 2L of supplemental oxygen would be administered via nasal cannula until the oxygen saturation would increase above 95%. In case of bradycardia, hypotension, apnea, decreased respiratory effort, over-sedation, and any signs of systemic destabilization, the procedure would be stopped, IV sedative drug administration would be ceased and appropriate resuscitation with airway control would be initiated.

The quality of sedation was assessed using the VAS and MAAS [7, 8] recorded at 4 events during the procedure. They were at IV cannulation, LA administration, incision, and suturing. All the values were charted and remarkable events during the procedure were also noted.

After the completion of the surgery, patients were shifted to the recovery room for post-operative management. All patients were observed for a minimum of 2 hours as a protocol. A modified Aldrete scoring system was used to assess the patients for discharge. A score of 10 was used to deem patients safe to be discharged along with the caregiver accompanying them.

In the postoperative period, quality and time of recovery were assessed using the modified Aldrete scoring scale. The satisfaction of the surgeon and the patient towards the performed procedure was assessed using the Numerical rating scale. The patients were again assessed using the State-Trait Anxiety Index 9 for the level of anxiety during discharge.

4. Results

A randomized double-blind prospective study was carried out which included 20 subjects. They were divided into 2 groups namely group I and group II. Group I received midazolam and group II received dexmedetomidine as an IV sedative agent. The study was carried out according to the study design mentioned earlier.

Owing to maximum cases of fracture fixation, 85% of patients treated were males. There was no statistical difference between the gender groups among any parameters included in the study.

The objective of the study was to compare the 2 drugs for quality of sedation, safety, and efficacy. The quality of sedation and efficacy was measured using subjective parametric scales and the safety of the drug was measured using objectives parameters such as the heart rate, blood pressure, respiratory rate, and oxygen saturation. Statistical data was compiled and analyzed using the SPSS version 23 software. The data did not follow a normal curve, and thus a Kruswal Wallis test was used to compare the qualitative data.

The quality of sedation was assessed using a patient-rated and a clinician rated scale intra-operatively. The assessment was quantified using these scales and noted at 4 different events during the procedure. The events were marked at the time of IV cannulation, local anesthesia administration, incision, and suturing. At IV cannulation, sedation and/or anesthesia is still not administered. Thus, the patients are expected to be anxious and relate to the events more painfully. After IV cannulation, the loading dose of the IV sedative agent is administered. The local anesthesia is given after the loading dose i.e., 10min; at this point the patient is expected to be more relaxed. The other two events at incision and suturing will represent the quality of sedation achieved during the procedure for a given dose of IV sedative administered.

The quality of sedation was compared using 2 scales which were used intra-operatively at 4 events during the procedure. They were marked at intravenous cannulation, local anesthesia administration, and incision and suturing.

One scale was the self-rating visual analog scale, which consists of a 10 cm line anchored at one end by a label ‘‘not anxious’’ and at the other end as ‘‘most anxious’’. There was no significant difference between the two groups, although patients who were administered dexmedetomidine seem to be less anxious during the maintenance phase compared to the midazolam group.

Another scale used to measure the quality of sedation was a clinician-rated ‘motor activity assessment scale’. Table 1 shows the scale and its measurements. Graph 2 shows the comparison between the two groups with respect to the MAAS score. MAAS 3 among the 2 groups was statistically significant, which means the patients in the midazolam group had lesser motor activity than in the dex group.

The efficacy of the drugs was compared using a numerical rating scale. The surgeon and the patient were asked about their experience with the procedure and quantified using the above scale. Graph 3 shows the comparison between the two groups. There was no significant difference between the groups. The patient satisfaction seems to be higher with the dex group and the surgeon preferred midazolam more.

The vital signs like heart rate, blood pressure, respiratory rate, and there was no significant difference between the groups in terms of quality of sedation. The patients were well sedated in both groups and none of the patients needed rescue medication.

There was no significant difference in the heart rate. The heart rate in group I remained almost similar to the baseline without much change. The group II patients did have a decrease in heart rate considerably but no patients required any intervention.

Though no significant difference was seen between the groups, patients in dex group clinically did have mild hypotension. It was not significant and no patient required any additional intervention.

There was no significant difference between the groups in terms of respiratory rate. Although patients given midazolam showed a decrease in respiratory rate such events were managed by stimulating the patient to breathe, and 2L oxygen via nasal cannula if necessary. No events needed assisted ventilation and airway control. The patient in the dex group showed a steady respiratory rate without much fluctuation from the baseline.

There was no significant difference in the oxygen saturations between the two groups. Clinically, the patient's given midazolam did have episodes of desaturations and apnoea. The oxygen saturation in these patients would generally decrease as the respiratory effort decreased, but this was not significant enough to intervene. All events were under control and managed by stimulating the patient to breathe, and oxygen delivery via nasal cannula if required. All patients responded to such stimulus and recovered within 1 -2 minutes. The surgeries were continued without interruption and were completed.

Table 1: Randomization of the patient

Sample for the study
• Patients visiting/referred to the department of Oral and maxillo-facial surgery at A J Institute of dental sciences who met the inclusion criteria for the proposed study.
• They were explained about the study, written informed consents taken and were included voluntarily after understanding the details pertaining to the study.
Method
• One of the investigators who are not directly involved in the treatment and management of the patient are chosen to spin the coin just before the patient is shifted to the operative room.
• On showing heads, the patient is allocated to group one and on showing tails the patient is allocated to group II. The anaesthetist is informed regarding the grouping of the patient, for which he would prepare the desired drug for administration. The patient and the operating surgeon are blinded grouping procedure.
• The patient would have already received complete information regarding both the drugs and the sedation procedure. A written informed consent would have already been taken by this time. .
Sample size and randomization technique
• Toss-A-Coin method was used to randomly allocate the patients to each group. Since the allocations of patients were not under the control of the researcher, the study was carried out until the sample size was received.
• A minimum of 20 patients were included in the study. They were divided into 2 groups having 10 patients each. Group I received midazolam and group II received dexmedetomidine as IV sedative agents

Table 2: Method of drug administration

	Drug	**Method of administration**	**Induction (10min)**	**Maintenance (90 min)**	**Desired sedation**	**Rescue drug (Infusion)**
Group I	Midaz	Bolus over 1 minute	1mg in 1cc NS	1mg in 1cc NS q 20min	RSS 3	Propofol
Group II	Dex	Infusion	1mcg/kg/hr	0.2 – 0.7 mcg/kg	RSS 3	Propofol

*Notes:

- Maximum dose: Midaz = 5mg, Dex = titrated against weight and desired sedation
- Rescue drug is used when the desired IV sedative agent has failed to induce sedation

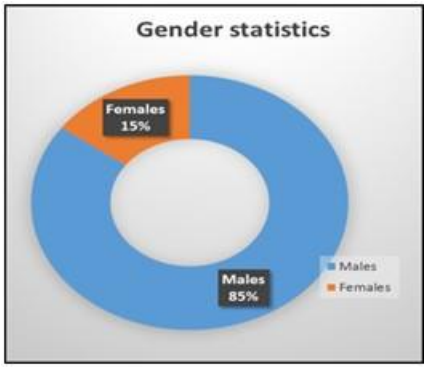
Table 3: Showing all the minor oral surgical procedures performed in the study

SL No	**Cases**	**No**	**Male**	**Female**
1	Parasymphysis fracture	11	10	1
2	Mini plate placement for orthodontic tooth movement in upper and lower jaw	2	2	0
3	Implant placement	2	1	1
4	Cyst enucleation with apicectomy	2	2	0
5	Ridge augmentation with bone graft + Implant placement	1	1	0
6	Impaction	1	0	1
7	Symphysis fracture	1	1	0
	Total	**20**	**17**	**3**

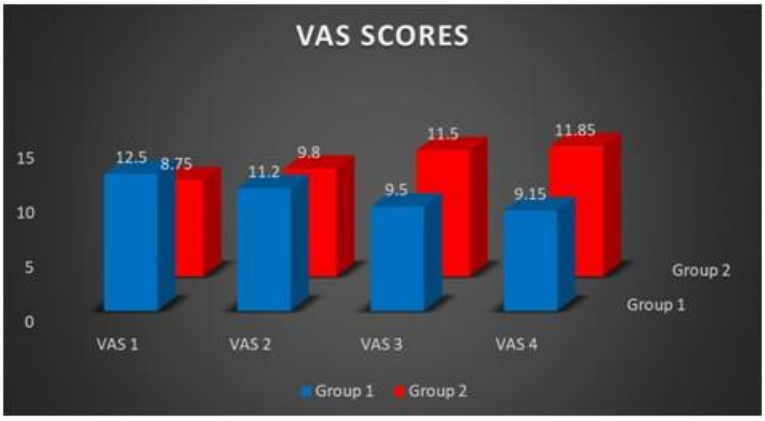
Table 4: MAAS system

Score	Description	Definition
0	Unresponsive	Does not move with noxious stimulus[a]
1	Responsive only to noxious stimuli	Opens eyes OR raises eyebrows OR turns head toward stimulus OR moves limbs with noxious stimulus[a]
2	Responsive to touch or name	Opens eyes OR raises eyebrows OR turns head toward stimulus OR moves limbs when touched or name is loudly spoken
3	Calm and cooperative	No external stimulus is required to elicit movement AND patient is adjusting sheets or clothes purposefully and follows commands
4	Restless and cooperative	No external stimulus is required to elicit movement AND patient is picking at sheets or tubes OR uncovering self and follows commands
5	Agitated	No external stimulus is required to elicit movement AND attempting to sit up OR moves limbs out of bed AND does not consistently follow commands (e.g., will lie down when asked but soon reverts back to attempts to sit up or move limbs out of bed)
6	Dangerously agitated, uncooperative	No external stimulus is required to elicit movement AND patient is pulling at tubes or catheters OR thrashing side to side OR striking at staff OR trying to climb out of bed AND does not calm down when asked

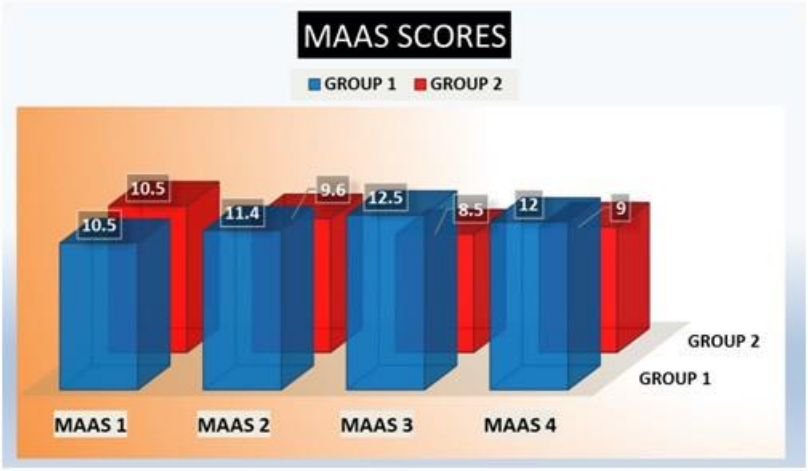
[a]Noxious stimulus, suctioning OR 5secs of vigorous orbital, sternal, or nail bed pressure.



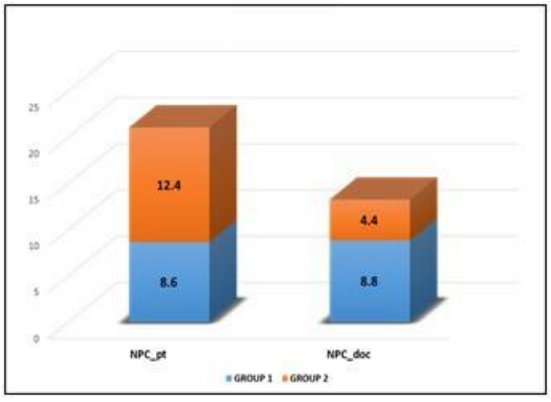
Graph 1: Showing the gender statistics



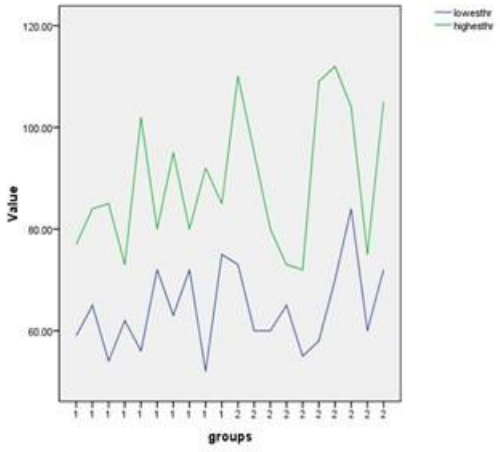
Graph 2: VAS scores



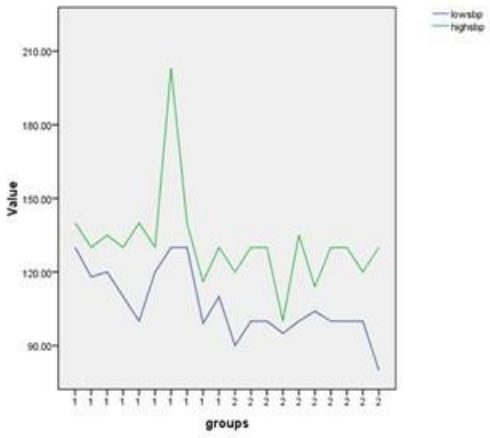
Graph 3: MAAS score



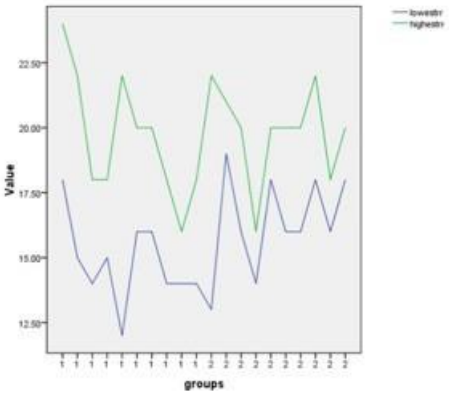
Graph 4: NRS



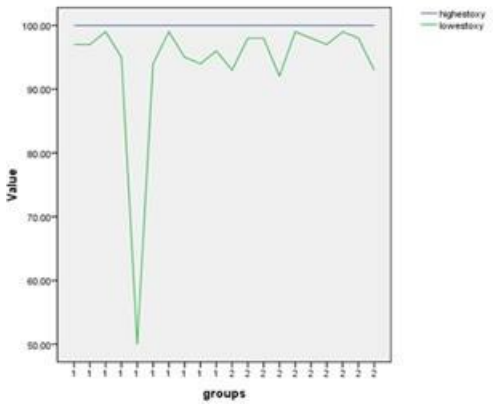
Graph 5: Vital signs – Heart rate



Graph 6: Vital signs – Systolic blood pressure



Graph 7: Vital signs – Respiratory rate



Graph 8: Vital signs – Arterial oxygen saturation

5. Discussion

The onset of action of intravenously administered drugs is the most rapid among all other routes. The arm-brain circulation time is approximately 20-25 seconds. Because of this reason, drug dosage may be tailored to meet the specific requirement. Drugs can be titrated against the required depth, quality, and safety limits of sedation. Since there are significant pharmacogenetic differences in sedative drug response it results in a large variation in dose requirements. Titration is obviously important to reduce the risk of over-sedation and the same was implemented in the protocol of this study.

The side effects of nausea and vomiting are extremely uncommon when drugs are administered intravenously as recommended. Other adjuvant drugs like control of salivary secretions, antacids, anti-emetics, and intravenous fluids can be administered via the same route which makes it a balanced procedure and prevents any untoward events. The gag reflex is diminished during sedation, which is an essential requirement for any procedure carried out in the oral cavity. A readily available IV access also makes it much more convenient in case of emergencies.

IV sedation requires more intensive monitoring and knowledge about the clinical actions of the drugs being used. Since the IV route acts immediately, any untoward effects of the drugs and related complications must be managed quickly. An uncomfortable aspect of IV sedation is the need for a painful procedure like venepuncture in the already anxious patient. Local complications at the site of IV injection like hematoma, phlebitis, and rarely intra-arterial injection of the drug could occur and must be managed diligently. Monitoring of patients receiving IV conscious sedation must be more intensive than that required in most other techniques.

Conscious sedation in oral surgical practice is constantly developing. Diazepam played a major role in intravenous sedation and, although still regularly used, it has largely been superseded by midazolam.

Midazolam remains the most widely used agent for procedural sedation [10]. For several years now, midazolam has been the mainstay of IVS in dentistry and oral surgery with predictable results. Midazolam is a 1, 4 benzodiazepine compound that is similar in most pharmacologic aspects to diazepam. The onset time for intravenous midazolam is 3 minutes. It is significantly shorter and more predictable than its predecessors. The targets for the benzodiazepine actions are the GABAA receptors. GABA is a major inhibitory neurotransmitter in the CNS. The binding of GABA to its receptor triggers an opening of the chloride channel which leads to an increase in the chloride conductance. This mechanism provides anxiolysis, and sedation, and is known for creating anterograde amnesia. Benzodiazepines also have a wide therapeutic index validating their safety in the outpatient setting.

The potential for a sedative with a different mechanism of action from a benzodiazepine may prove to be beneficial for surgeons and dentists. Dexmedetomidine is a fairly recent drug used for procedural sedation with an emphasis on oral surgery and dental procedures. Unlike most anesthetics that affect the GABA receptor, its mechanism of action is to activate the alpha-2 adrenergic receptor. The consequence is a reduction in noradrenergic neurotransmitter release and depression of adrenergic pathways.

This occurs because the alpha-2 receptor is predominantly pre-synaptic and activates a member of the guanine nucleotide-binding protein (G-protein) coupled signaling system. Activation of alpha-2 receptors increases the inhibitory G-protein, Gi, and reduces cyclic adenosine monophosphate (cAMP). The reduction in the second messenger cAMP results in sequestration of calcium ions and reduces the synapse from releasing stored neurotransmitters from its vesicles.

The alpha-2 receptor is not ubiquitous but is found in certain areas within the brain. An area that is believed to provide the sedative effects of Dexmedetomidine is known as the Locus ceruleus. The Locus Ceruleus is located within the brain stem and it receives and transmits multiple innervations to and from many regions within the brain. The Locus Ceruleus has been shown to be involved in circadian wake and sleep cycles as well as a center for the management of stress responses. During wakefulness, the locus ceruleus has a high adrenergic output which decreases during deeper levels of sleep. Therefore, the action of Dexmedetomidine is unique in that it produces sedation in a manner similar to natural sleep. Stress also increases adrenergic outflow within the locus ceruleus.55

The pathways for stress response are not clearly understood. There are two mechanisms by which Dexmedetomidine produces analgesia involving activation of presynaptic alpha 2 receptors in the spinal cord. One is by direct activation of the descending inhibitory pain pathway; the other is by inhibiting the release of substance P.55

The different mechanism of action of Dexmedetomidine from Midazolam may help reduce some of the adverse side effects seen with Midazolam. For example, Midazolam is well known to cause

restlessness and disinhibition instead of sedation in some patients, and this is referred to as a paradoxical reaction which includes increased talkativeness, emotional release, excitement, excessive movements, and even violent behavior. Surgery will then become extremely difficult, and patients may require flumazenil for reversal.55

The paradoxical reaction creates a situation where the surgeon now faces an increasingly difficult condition to perform the operation. Though such episodes were not encountered in our study, they have been well documented in the literature. Although the mechanism by which this occurs is not fully understood, the risk factors for the paradoxical reaction include children, the elderly, and in patients with a history of alcohol abuse and aggressive/anger behaviors. The incidence of this phenomenon has been reported between less than 1% to over 10% of patients. 55 In a review, reported by Chang et al one incidence of excessive movement and restlessness after the administration of midazolam was noticed. Although they did not call the incident a paradoxical reaction, their description of the event is consistent with paradoxical reactions. This one incident represents a minor percentage in their study of all the patients in our review who received midazolam, this may have been underreported since it is difficult to diagnose. Some studies used Propofol and/or Fentanyl as a rescue and thus did not allow any agitation to continue. This is in comparison to Dexmedetomidine which had no reports of agitation after administration. It demonstrates that Dexmedetomidine may be beneficial in certain cases where patients present the risk factors for this paradoxical reaction, although further studies are needed.

Midazolam can cause respiratory depression whereas dexmedetomidine appears not to. Whilst respiratory rate did not differ significantly between groups in our study, oxygen desaturation (SaO2 < 90%) did occur in both groups. As both drugs potentially can reduce muscle tone and lead to upper airway obstruction, at doses that produce moderate sedation this effect may be more contributory than respiratory depression to desaturation. All desaturated patients responded to verbal stimulus and low flow oxygen therapy.

Ramsay sedation score was used to assess the depth of sedation and RSS score 3 was depth as the endpoint for depth of sedation in this study. The sedation was titrated to reach this depth intra-operatively. All patients receiving dexmedetomidine and midazolam reached an RSS of three though in the midazolam group it took a longer time whereas the dex group reached the desired sedation immediately after the infusion.

The quality of sedation was assessed by 2 scales as mentioned above. Both the scales were used intra-operatively at 4 events during the procedure. The was no significant difference in the quality of sedation between the two groups except during the incision, group 1 showed the higher quality of sedation with the MAAS system. Since the scale used was rating the movement of the patient, midazolam caused sedation with minimal movement of the patient as compared to dexmedetomidine with produced sleep-like sedation. Thus, any stimulus like the sound of instruments would awake the patient causing some mild movements. The VAS scores given by the patients of group II were slightly higher than that was a group I, though they were not statistically significant, we can assume they were more relaxed as compared to group I patients. Midazolam is also known to cause anterograde amnesia, which was not tested in this study. This property of midazolam could be favorable or unfavorable depending on the patient since some patients do feel uncomfortable when they cannot remember the events and experience loss of memory. Amnesia may or may not be an advantage to patients. Some may wish to avoid the recall of unpleasant experiences in surgery, but others dislike having memory loss. It is well known that midazolam has a potent anterograde amnesic effect. On the other hand, dexmedetomidine infusion also results in impairment of memory and psychomotor performance. We did not test for such properties of either drug in our study.

The efficacy of the drug was assessed using the NRS. In our study, though there was no statistical difference between the groups, it was seen that the surgeons preferred midazolam sedation, and the patients referred to greater comfort with dex. After surgery, most patients in both groups were satisfied with their sedation and would be happy to have the same anesthetic care (as opposed to general anesthesia or local anesthetic alone) in the future. Both the drugs appear to be equally acceptable to patients, although this could only be truly evaluated with a cross-over comparison. Rapid recovery is desirable after sedation and short surgery. The patient's performance was completely restored two hours postoperatively, which confirms that both drugs are applicable to day surgery. Some of our patients stayed overnight in the hospital after surgery because of surgical reasons. Neither drug had an advantage in reducing side effects such as dizziness, nausea, and vomiting.

The safety of the drug was measured by the ability of the drugs to maintain the baseline vitals and produce a desired depth and quality of sedation. There was no statistical difference in the variability of the vital signs between both the groups although there were few clinically significant differences between the two drugs used. Dex depressed the cardio-vascular function during the induction dose causing a decrease in heart rate and blood pressure of about 15% from the baseline. No patients needed any additional anti-cholinergic, vasopressor drugs to counter the effects of dexmed, as the decrease was not clinically significant. The vitals remained stable throughout the procedure and return back to baseline in about 2 hours postoperatively in most cases. The effects of dex were seen last longer than midazolam in a few patients, who required about 4 hours for complete recovery. Midazolam on the other hand did not cause any depression in the cardio-vascular system but depressed the respiratory effort. Though there were no patients who needed resuscitation and ventilation support, there were

episodes of apnoea followed by a reduced respiratory rate in group I. All patients with such events recovered with mild stimulation, and the procedure was continued as planned without interruption.

There was 1 episode in group one when the saturation dropped to 50%, at which point the procedure was temporarily stopped, patients were stimulated to increase their respiratory rate and were started on 2L oxygen via nasal cannula. The patient recovered in less than 2 minutes and the procedure was carried out uneventfully. In comparison, Dexmedetomidine causes an increase in arterial pressure upon rapid bolus infusion 19. This is due to direct effects on vascular alpha-1 receptors. In our study, we did see an increase in arterial blood pressure initially after a loading dose of dex in a few patients alone. This was minimized in our study by slowly infusing the drug over 10 minutes for the loading dose, but this will take more time to reach the sedation endpoint when compared to midazolam, which can be given as a bolus. After infusion of dexmedetomidine, blood pressure, heart rate and cardiac output decrease slightly. In our study, there was no cardiovascular instability requiring intervention. The effects of alpha-2 agonists on the cardiovascular system may be beneficial in high-risk patients. Pain on local anesthetic infiltration can be a stressful experience and pain after dental surgery may be considerable.

The analgesic properties of dexmedetomidine have been demonstrated in healthy volunteer studies, but controversy still exists in clinical practice. When it is used preoperatively or intra-operatively, the analgesic consumption can be reduced without lowering the pain scores. We did not test for this hypothesis in our study.

In order to evaluate Dexmedetomidine as a potential substitute for Midazolam a systematic review of articles was done that evaluated these two drugs as sole agents for intravenous moderate conscious sedation. In the articles reviewed, there appears to be a consensus that Dexmedetomidine is a suitable substitute for Midazolam for intravenous moderate sedation. All of the articles reported the ability of Dexmedetomidine to achieve adequate sedation levels similar to Midazolam. Three variables were evaluated to help determine the quality of sedation, the need for rescue, patient satisfaction, as well as surgeon satisfaction.

Apan A et al found that similar numbers of patients in the saline, Dexmedetomidine, and Midazolam groups required rescue for cataract surgery, whereas Cheung et al did not require rescue for any of their dental patients. This may be due to the fact that Apan et al used a very small dose of Dexmedetomidine and Midazolam. The standard regimen for Dexmedetomidine administration requires a 0.2 – 1 mcg/kg bolus given over 10 minutes and a continuous infusion at 0.2 – 0.7 mcg/kg/hr. This was the regime used in our study too.

Apan et al chose to administer 0.25 mcg/kg/hr, which is in the low range of this recommendation. The reasoning was that their patient population was much older than in other studies and a high loading dose predisposed patients to hypotension and bradycardia. Yet by administering Dexmedetomidine in this fashion, they found that 6 patients in the Dexmedetomidine and 10 patients in the Midazolam groups required intraoperative changes in dosing. Despite increases in anesthetic dosing, they found that 3 patients in the Dexmedetomidine and 4 in the Midazolam groups could not reach a BIS value of 85 or less. Alhashemi also evaluated Dexmedetomidine and Midazolam for cataract surgery. Their average patient age was slightly younger (61 years old vs 65 years old), but they used an initial loading dose of 1 mcg/kg of Dexmedetomidine and titrated the continuous infusion starting at 0.4 mcg/kg/hr. Although there was a decrease in heart rate and mean arterial pressure compared with Midazolam, none had bradycardia (HR < 60) or hypotension (MAP < 60 mmHg), and no one required intervention. As well, none of the patients required Propofol as a rescue. This was a similar finding in our study.

A paper by Kasuya Y et al [9] evaluated BIS values for dexmedetomidine sedation compared with an observational sedation assessment scale, Observers Assessment of Alertness and Sedation Scores (OAA/S). They found that an OAA/S score of 4 corresponded to an average of 62 BIS index (range 53.5 – 68.5). BIS values can also be highly variable, both inter-individual as well as intra-individual and may be affected by illness.

Other methods of evaluating the level of sedation include observational scales such as the RSS. This method was employed by Cheung CW et al, Ustun Y et al, Kaya FN et al, and Alhashemi JA. An initial bolus of 1 mcg/kg for 10 minutes was sufficient to sedate a patient to an RSS value of 3 or 4. This was similar to a 0.02 mg/kg bolus or 5 mg infusion (over 10 minutes) of Midazolam. Patients within these studies were equally satisfied with either Dexmedetomidine or Midazolam with some favoring Dexmedetomidine sedation. Patient satisfaction is completely subjective. A way to objectively quantify patient satisfaction is to have patients describe their experience using an ordinal scale. The Visual Analog Scale, the Numerical Rating Scale, and the Likert-Like scales are all ways for patients to quantify their experiences. The three methods for measuring subjective outcomes are commonly used in research. They are also valid and reliable measures and some authors prefer the Likert-like system as it is typically easy to complete and easy to interpret. Patients tend to prefer Dexmedetomidine sedation over Midazolam for cataract surgery. Patients who received 1mcg/kg bolus in Alhashemi's paper rated their sedation as somewhat satisfied using the likertlike sedation score.

Apan et al had a simple, yes, no, or no comment to the statement: "I would have the same procedure when required". Although they did not provide statistics for this portion of their study, they concluded in their discussion that patients seemed more satisfied with the Dexmedetomidine sedation. The best indication for patient satisfaction was reported by Ustun et al. Ustun et al designed a cross-over randomized control trial for the removal of third mo-

lars. In this study, study participants were able to experience both Midazolam and Dexmedetomidine sedation and then reported their satisfaction using the VAS. They found a statistical significance in the VAS, but to clinically qualify it, they found that a greater proportion of patients would choose the Dexmedetomidine sedation over the Midazolam sedation if they were to have the same procedure done again. The lack of difference seen in other papers may be due to the fact that patients were not able to base their decision on experiencing both types of sedation.

The analgesic effect of Dexmedetomidine is not one of the key outcomes that were evaluated, but it deserves some mention. Ustun et al reported that 75% of patients sedated by Midazolam demonstrated a reaction to pain during an intraoral injection while only 30% reacted when sedated by Dexmedetomidine. This is in contrast to Cheung et al who reported no difference between groups in response to local anesthesia injection, pain in the postoperative ward, and three days after discharge. The time to request the first analgesic and analgesic consumption was similar between groups. An explanation for this discrepancy may have to do with the sample size and sensitivity of their pain rating system. Their study was focused on patient satisfaction using the Numerical rating system and not pain. Their pain scores had a much larger range and IQR than patient satisfaction and so a larger number may have found significance. Kaya FN also reports that Dexmedetomidine prolongs the effects of bupivacaine spinal anesthesia as measured by the time to first request analgesics as well as analgesic requirements postoperatively.

Likewise, surgeons found Dexmedetomidine to be equal to Midazolam in providing adequate sedation. Demiraran JA stated that endoscopists rated the Dexmedetomidine sedation higher in satisfaction than Midazolam sedation. As well, they also noted less retching while sedated with Dexmedetomidine. Unfortunately, the endoscopists were not blinded to the type of sedation and therefore the results are less reliable than if they were blinded.

Only six out of 117 articles were identified as appropriate for this review since they were used in oral surgery or dental procedures. The small number of articles that qualified for our systematic review may indicate that these drugs typically have not been used as sole agents for sedation, but combined with other agents such as a narcotic or Propofol. Another factor for a small number of articles is the fact that Dexmedetomidine is also used within the intensive care unit. In this scenario, patients require sedation to tolerate intubation and are typically in a critical condition such that only minimal anesthetic is necessary. This situation does not portray the environment that oral surgeons/dentists would typically face within their practice.

Our study demonstrates that dexmedetomidine can provide comparable sedation when compared to midazolam for minor oral surgical procedures under local anesthesia. A lower heart rate and blood pressure, as well as less amnesia, can be achieved by using dexmedetomidine.

6. Conclusion

Many studies have been done to evaluate dexmedetomidine and midazolam and they have been compared to others drugs mostly when used in combination. The present study was an attempt to study these drugs individually, and compare their efficacy and safety when used as single-agent IV sedatives in minor oral surgical procedures. This gives surgeons and patients a better method of managing pain, fear, and anxiety.

Both the drugs were efficient and safe in producing the required sedation. In conclusion, dexmedetomidine is a comparable alternative to midazolam for sedation in minor oral surgery under local anesthesia. It is the preferred drug when a lower heart rate and blood pressure, with lesser amnesia, is desired. Midazolam on the other hand could be used safely in patients with a high vagal tone, and patients with cardio-vascular depression among other situations where dex would not be an ideal sedative to use.

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