Anesthetic Adjuvant Effect of Dexmedetomedine versus Midazolam and Recovery Profile: Clinical and Electroencephalographic Study


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Abstract

Background: Many surgical procedures would not be possible without anesthesia or sedation. The goals of anesthesia or sedation are a reversible loss of consciousness with a lack of movement, a lack of awareness or recall, and unresponsiveness to painful stimuli. Inadequate anesthesia or sedation may lead to intraoperative awareness with recall or to prolonged recovery and increased risk of postoperative complications for the patients [1].

Objective: Comparing the sedative, the anesthetic adjuvant effect and the recovery profile of dexmedetomedine versus midazolam as premedicants in minor surgeries.

Patients and Method: Eighty adult patients of American society of anesthesiologists physical class I (ASA I), aged 20-50 years old, were randomly allocated into two equal groups (n=40) each patient received intravenous IV 0.04 mg/kg midazolam (Group M) or IV 1 μg/kg dexmedetomidine (group D) over 10 minutes. Perioperative bispectral index BIS readings, sedation score and recovery times.

Results: Bispectral index BIS readings were also lower in group D than group M with high significance (p-value <0.001**) except at 60th minute intraoperative no significant difference noticed. Recovery times were shorter with high significance (p-value<0.001**) in group D than group M. No history of recall of events or intraoperative awareness were recorded in both groups.

Conflict of Interest: There is no conflict of interest

Conclusion: Dexmedetomedine was found to be a safe anesthetic adjuvant drug with superiority over midazolam, because Dexmedetomedine allows deeper anesthesia planes but with shorter recovery times in comparison to midazolam.

Key Words: Depth of anesthesia – Bispectral index – Recovery profile.

Introduction

ACCORDING to Prys-Roberts, common feature of general anaesthesia is suppression of conscious perception of noxious stimuli. Analgesia, autonomic stability and muscle relaxation are desirable but not actual components of anaesthesia. Prys-Roberts divided the noxious stimuli into somatic and autonomic components, which were further, divided into sensory, motor and respiratory, haemodynamic, pseudomotor and hormonal [2]. A gradually increasing concentration of general anaesthetic agent produces a progressive decline in the ability of the brain to carry out tasks and to remember these afterwards. The effect of anaesthesia on cognition and memory occurs before noticeable autonomic effects [3].

Depth of anaesthesia is a clinical term that accounts for both diverse drug effects and diverse clinical needs. Adequate depth of anaesthesia occurs when the concentrations of the agents are sufficient to produce the effects needed for the comfort of the patient and the conduct of surgery. There are both subjective and objective methods of assessing depth of anaesthesia. Subjective methods rely on the movement and autonomic response to stimuli and depend on the opinion and experience of an anaesthesiologist. The objective methods rely on the sensitivity of the monitor [4].

In October 1996, bispectral index (BIS) achieved approval by the Food and Drug Administration as the first electroencephalogram (EEG)-based monitor of anaesthetic effect. BIS reduces complex EEG processing to a simple number ranging from 0 to 100. BIS decreases with increasing depth of anaesthesia and adequate level of anaesthesia is achieved with BIS ranging from 40 to 60 [5].
Table (1): Method of assessment of depth of anesthesia [4].

A - Subjective methods:
1- Autonomic response
   - Hemodynamic changes
   - Lacrimation
   - Sweating
   - Pupillary dilatation
2- Isolated forearm technique

B - Objective methods:
1- Spontaneous surface electromyogram (SEMG)
2- Lower oesophageal contractility (LOC)
3- Heart rate variability (HRV)
4- Electroencephalogram and derived indices
   - Spectral edge frequency
   - Median frequency
   - Bispectral index
5- Evoked potentials
   - Auditory evoked potentials
   - Visual evoked potentials
   - Somatosensory evoked potentials
   - Auditory evoked potential index

BIS is now considered to have a reliable predictive power of adequate anaesthetic depth and preoperative sedation, thus could guard against the occurrence of major haemodynamic events during the induction period [8].

Sedative drugs control anxiety besides reducing the sympathetic discharge. Controlling anxiety provides comfort to the patient. This characteristic of sedative premedication agent is their desired property [6,7].

One of the drugs popularly used for sedation is midazolam, it is an agonist at the benzodiazepine receptor-α subunit of the central neuroinhibitory gamma-aminobutyric acid-A receptors. Midazolam can be administered as an intravenous (i.v) bolus or as a continuous infusion, and its desirable clinical effects range from anxiolytic to hypnotic depending on the percentage of receptor occupancy rather than plasma concentrations of the drug [8]. The sedative, hypnotic, and amnestic properties of benzodiazepines have been used as an adjunct to opioids [8], but with consideration of more respiratory depressant effect and prolonged recovery time [9].

Another group of drugs with favourable effect on stress response is The α2-adrenergic agonists. Dexmedetomidine is a more specific and selective α2 agonist with 10-fold greater α2/α1-receptor selectivity and has a shorter duration of action than clonidine. It produces dose-dependent sedation and analgesia. These properties make it theoretically a suitable agent for use as a part of an anaesthetic regimen. In patients having non cardiac surgery, perioperative administration of dexmedetomidine decreases the need for anaesthetics [10].

The adjuvant anaesthetic effect of dexmedetomidine is well appreciated, and had been investigated in diversity of patient populations and most studies rendered consistent results that dexmedetomidine decrease anaesthetic requirements [11,12].

Patients and Methods

This randomized prospective study was carried out after approval of the institutional ethics committee and obtaining written informed consents. The patients were operated upon El-Agouza Police Hospital from May 2012 till November 2014.

Inclusion criteria:

Eighty adult patients scheduled for direct laryngoscopic surgical procedure were included in the study. All patients were between the ages of 20-50 years old, of both sexes, weight 50-100kg and American Society of Anesthesiologist (ASA) physical classes I.

Exclusion criteria:

Patient refusal, hypertension, hepatic disease, renal disease, patient with coagulation defects, chest diseases and cardiac diseases. Procedural time more than 1 hour, patients received any narcotic or sedation in the last 24hrs before the operation, neck dissection planned after direct laryngoscopy D.L., known history of allergy to any drug used in the study and patient with obstructive sleep apnea syndrome.

Patients were randomly allocated (closed envelop randomization) into two equal groups (n=40) and all measures were made by an observer blinded to the patient’s group:

Dexmedetomedine group (group D): (n=40)
Every patient received IV 1 µg/kg dexmedetomidine (Precedex® dexmedetomedine HCL 100 µg/ml 2ml vial Hospira. Inc.) in 20mL serum saline set up to be infused in 10 minutes.

Midazolam group (Group M): (n=40)
Every patient received IV 0.04mg/kg midazolam (Mediathetic® midazolam 5mg in 1ml ampoul. Amoun. Inc.) diluted in 20ml saline set up to be infused over 10min before anaesthesia induction.

Patient preparation:

All patients were cannulated with 20G cannula in a peripheral vein in the preparation room. The BIS monitor electrodes (Cerebral State Monitor. Model CSM 2) and Standard monitors (ECG-pulse...
oximeter-non invasive blood pressure monitor cuff) were applied to every patient. Moreover, use of the bispectral index intraoperatively in the current study was mainly to assess the drugs adjuvant effect on the depth of anesthesia and sedation. Then the premedication was given as described. The patient was transferred to the operating room. Both groups had the same technique of anesthesia.

**Induction:** Preoxygenation with 100% oxygen O₂ was initiated for 5 minutes then anesthesia induction by Propofol 2mg/kg (propofol 1% Fresenius Kabi Austria Gmbh 20ml), lidocaine 1mg/kg and fentanyl 1 µg/kg (fentanyl Haemeln. 2ml 50 microgram/ml of fentanyl citrate) then muscle relaxation was induced by atracurium besylate 0.5mg/kg. After sufficient muscle relaxation, endotracheal intubation was done.

Mechanical ventilation was initiated by tidal volume 10ml/kg, frequency 10 per minute with 50% O₂ and 50% air.

**Maintenance:** Loss of consciousness was maintained by end tidal sevoflurane 2% all through the procedure.

**Fluid balance:** All patients received 10ml/kg /hour crystalloid ringer acetate.

**Recovery:** At the end of the surgical procedure, sevoflurane was turned off and spontaneous respiratory effort were observed. When the patients' spontaneous respiration became regular, tidal volume 6ml/kg and oxygen saturation above 97% and BIS reading above 90 (intact reflexes) extubation was performed. Extubation time was determined and recorded as the time from turning off the sevoflurane until extubation. Time of spontaneous eye opening, eye opening to verbal command, place, person and time orientation were measured and recorded. Then the patient was transferred to the post anesthesia care unit (PACU) for one hour.

**Outcome parameters:**

The degree of sedation was assessed by Ramsay sedation scale [13] twice. preoperative immediately after giving the test drug and postoperative assessment was done at 10th minute in the recovery period. BIS reading before sedation, after sedation, at time of intubation then every 15 minutes intraoperative till full recovery.

Recovery times were assessed since turning off sevoflurane in the form of extubation time, time of eye opening to verbal stimulus, time of spontaneous eye opening and place, person and time orientation in the PACU. All the patients were questioned for history of awareness and recall of events at 4 hour postoperatively. Perioperative side effects as; nausea, vomiting, bradycardia hypotension, tachycardia, hypertension, hypotension, laceration, pupillary dilatation, arrhythmias, hypoxia, laryngeal spasm, cough, agitation, pain and shivering were recorded. Percentage of patients who received vasoactive drugs to maintain hemodynamic stability.

**Table (2): Ramsay sedation scale.**

<table>
<thead>
<tr>
<th>Sedation level</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is anxious and agitated or restless, or both</td>
<td>1</td>
</tr>
<tr>
<td>Patient is co-operative, oriented, and tranquil</td>
<td>2</td>
</tr>
<tr>
<td>Patient responds to commands</td>
<td>3</td>
</tr>
<tr>
<td>Patient exhibits brisk response to light glabellar tap or loud Auditory stimulus</td>
<td>4</td>
</tr>
<tr>
<td>Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus</td>
<td>5</td>
</tr>
<tr>
<td>Patient exhibits no response</td>
<td>6</td>
</tr>
</tbody>
</table>

**Statistical methods:**

Sample size was calculated using Epicalc 2000 software. Using data from previous study, 80 patients were sufficient to carry out the study. Type I error (α) =5% with confidence level 95%, study power 90% (power of test) with type error II 10% (Beta). The significance level was at an (± value of 0.05). SPSS V17 computer software was used for statistical analysis. Data was presented as mean (±SD), median (range) or number (%) as appropriate. Comparison between the two groups was performed using unpaired Student’s t-test. Sedation scores were compared between the two groups using Mann-Whitney test. Intragroup comparison relative to baseline was performed using paired t-test. Categorial data were compared using Chi-square test (Fisher exact test) as appropriate. A p-value <0.05 was considered significant.

**Results**

1- **Sedation score in the two studied groups:**

Sedation was assessed by Ramsay sedation score twice; preoperative immediately after administration of the drug and postoperative at 10th minute during the recovery period. There were no significant differences in the sedation level after administration of the drugs preoperatively in both groups. Postoperatively in the recovery both groups continued to be around the same level of sedation with no significant difference, as shown in Table (3).
Table (3): Ramsay sedation score assessment in the studied groups.

<table>
<thead>
<tr>
<th>Ramsay Sedation score</th>
<th>Group D (dexmedetomidine)</th>
<th>Group M (midazolam)</th>
<th>Mann-Whitney Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Mean rank</td>
</tr>
<tr>
<td>Pre operative after sedation</td>
<td>2.3</td>
<td>0.0</td>
<td>40.54</td>
</tr>
<tr>
<td>Post operative</td>
<td>3.2</td>
<td>0.0</td>
<td>40.46</td>
</tr>
</tbody>
</table>

IQR: Inter quartile range. Non Sig. >0.05 Sig. <0.05* High Sig. <0.001**

2- Bispectral index (BIS):

In group D the BIS readings decreased with high significance ($p$-value <0.001) to (70.2±9.04) after sedation compared to the base line (96.7±2.03). At intubation BIS readings decreased to (54.3±5.92) and still highly significant lower than the base line. Intraoperatively BIS readings remained high significantly lower than the base line readings ($p$-value <0.001), as shown in Table (4) and Figs. (1,2).

In group M BIS decreased to (76.7±8.47) with high significance ($p$-value <0.001) after sedation in comparison to the baseline (96.4±1.98). At intubation BIS readings decreased to (57.8±6.01) and still highly significant lower compared to the base line values. Intraoperatively BIS readings remained lower with high significance compared to the base line readings ($p$-value <0.001), as shown in Table (4) and Figs. (1,2).

On comparing between the two groups there was no significant difference between BIS values before sedation. After sedation BIS readings were significant lower in group D than group M ($p$-value <0.05). At intubation group D still had lower BIS reading than group M with statistical significance ($p$-value <0.05). Intraoperative group D had highly significant low BIS readings at 15,30 and 45 minutes than group M, but at 60 minutes intraoperatively there was no significant difference between both groups), as shown in Table (4) and Figs. (1,2).

Table (4): Bispectral index BIS readings in the two studied groups.

<table>
<thead>
<tr>
<th>Bispectral index</th>
<th>Group D</th>
<th>Group M</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>t</td>
<td></td>
</tr>
<tr>
<td>Before sedation</td>
<td>96.70±2.03</td>
<td>96.40±1.98</td>
<td>0.669</td>
<td>0.506</td>
</tr>
<tr>
<td>After sedation</td>
<td>70.20±9.04</td>
<td>76.70±8.47</td>
<td>3.317</td>
<td>0.005*</td>
</tr>
<tr>
<td>At intubation</td>
<td>54.30±5.92</td>
<td>57.80±6.01</td>
<td>2.624</td>
<td>0.010*</td>
</tr>
<tr>
<td>At 15min intraoperative</td>
<td>49.00±6.16</td>
<td>55.60±8.90</td>
<td>3.856</td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>At 30min intraoperative</td>
<td>49.80±6.07</td>
<td>58.30±6.75</td>
<td>5.921</td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>At 45min intraoperative</td>
<td>52.67±6.88</td>
<td>60.71±3.11</td>
<td>5.743</td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>At 60min intraoperative</td>
<td>57.00±10.15</td>
<td>58.00±0.00</td>
<td>0.193</td>
<td>0.849</td>
</tr>
</tbody>
</table>

Paired t-test

<table>
<thead>
<tr>
<th></th>
<th>BS &amp; AS</th>
<th>BS &amp; AT</th>
<th>BS &amp; 15MIN</th>
<th>BS &amp; 30MIN</th>
<th>BS &amp; 45MIN</th>
<th>BS &amp; 60MIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

Non Sig. >0.05 Sig. <0.05* High Sig. <0.001**
3- History of recall of events:

In both groups no patient experienced recall of events or intra operative awareness.

4- Recovery times:

All of the recovery times were calculated since turning off the sevoflurane in minutes, it includes:

a- Extubation time.

b- Time to eye opening to verbal command.

c- Time to spontaneous eye opening.

d- Time to place, person and time orientation.

A- Extubation time:

In group D extubation time (9±1.63) was shorter than group M (13.9±2.46) with high significance (p-value <0.001), as shown in Table (5) and Fig. (3).

B- Eye opening to verbal command:

In group D eye opening to verbal command time (11.2±1.68min) was shorter than group M (16.9±3.83min) with high significance (p-value <0.001), as shown in Table (6) and Fig. (3).

C- Time to spontaneous eye opening:

In group D spontaneous time to eye opening time (13.4±1.71min) was shorter with high significance (p-value <0.001), than group M (18.9 ± 3.86min) as shown in Table (7) and Fig. (3).

D- Person, place and time orientation (PPT):

In group D PPT time (20.2±2.43min) was shorter with high significance (p-value <0.001) than group M (24.7±3.57min), as shown in Table (8) and Fig. (3).
Discussion

Midazolam is the most commonly used sedative in adults. It provides potent sedation, loss of memory and anxiolysis, while dexmedetomidine is a selective α2-adrenergic receptor agonist and presents dose-dependent decreased HR and BP, sedative anxiolytic and analgesic effects [5,8].

However, the quality of sedation of dexmedetomidine appears to be unique in comparison with GABAergic agents such as midazolam or propofol. Arousability is maintained at deep levels of sedation, with good correlation between the level of sedation (Richmond agitation-sedation scale) and the bispectral index (BIS) [14].

Dexmedetomidine induces sleep by activating endogenous non-rapid eye movement sleep-promoting pathways. Stimulation of alpha-2A receptors in the nucleus ceruleus inhibits noradrenergic neurons and disinhibits gamma-aminobutyric acid (GABAergic) neurons in the ventrolateral preoptic nucleus (VLPO). In contrast, GABAergic agents, such as propofol or benzodiazepines, directly enhance the inhibitory effects of the GABAergic system at the VLPO. Norepinephrine release from the locus ceruleus remains unaffected, thus leading to less restfull sleep [15].

BIS is now considered to have a reliable predictive power of adequate anaesthetic depth, thus could guard against the occurrence of major haemodynamic events during the induction period [16]. Both drugs in the current study were efficient concerning the depth of anesthesia, as BIS readings of both groups were below 60 (the deep zone of anesthesia suitable for surgical stimulation). Moreover dexmedetomedine readings were significant lower than midazolam readings.

Mansour et al. [17] studied dexmedetomidine versus midazolam as anesthetic adjuncts in off-pump coronary artery bypass surgery (OPCAB) with monitoring by BIS for the depth of anesthesia. They found that dexmedetomidine reduced sevoflurane anaesthetic requirements. The adjuvant anaesthetic effect of dexmedetomidine is well appreciated, and had been investigated in diversity of patient populations and most studies rendered consistent results that dexmedetomidine decreased anesthetic requirements [18]. Mansour et al. [17] found BIS readings of adequate anaesthetic depth were achieved among both groups at all time points of data collection. In Mansour et al. [17] study, sufentanil infusion and test drug (dexmedetomidine in group D and midazolam in group M) were standardized among both groups and the target BIS

![Graph showing recovery times](image-url)
value was solely achieved by manipulations of end tidal sevoflurane concentration. Thus the adjuvant anaesthetic effect of dexmedetomidine can be considered superior to that of midazolam, as BIS values achieved with dexmedetomidine were comparable to those of midazolam but at lower sevoflurane concentrations. In the current study end tidal sevoflurane was fixed to 2% so the adjuvant anesthetic effect of dexmedetomidine or midazolam expressed by the BIS readings which were lower significantly in dexmedetomidine group than the midazolam group.

In the current study there was no significant difference between dexmedetomidine group and midazolam group in degree of sedation which was assessed by Ramsay sedation scores. In agreement with the current results McCutcheon et al. [9]; found no difference in the degree of sedation between both groups, also Isik et al. [20] found no difference in Ramsay sedation score between the two studied groups before and after the sedation. That is considered in agreement with the current study finding. Alhashemi et al. [21]; found that although both drugs were effective in providing adequate intraoperative sedation, dexmedetomidine group patients were more satisfied with their sedation than those in midazolam group. This could be explained by the additional analgesic property of dexmedetomidine that could have contributed to improved patients’ perception of this form of sedation, and in part, by potential differences in the quality of sedation of the two drugs.

In the current study recovery times (extubation time, spontaneous eye opening, eye opening to command and ppt orientation) were significantly shorter in dexmedetomidine group than midazolam group. That may be explained as dexmedetomidine is unique in the fact that patients can be aroused readily, and when left unstimulated, they return to a sleep-like state [10]. Hall et al. [22]; found that the patients who received dexmedetomidine in the recovery room were more sedated when compared with the shorter-acting propofol. However, they were easily aroused to perform the psychomotor testing. This is consistent with one of the more interesting characteristics of dexmedetomidine, which is the ability to achieve sedation but preserve patient arousability. Through its action on pre- and postsynaptic alpha-2 receptors, dexmedetomidine reduces transmission across the synapse. Since noradrenergic output from the locus cerulus plays a vital role in arousal, reduced norepinephrine output resulting from dexmedetomidine infusion results in anxiolysis and sedation. This ability of dexmedetomidine to modulate locus cerulus activity is more than a neuroanatomic curiosity: It may explain how it can produce sedation without obscuring cognitive function.

Isik et al. [20] found no difference between dexmedetomidine and midazolam in place, person and time orientation which may need further studies in that.

In contrast to the current results An important finding, in Alhashemi’s [21] study, was the delayed readiness for recovery room discharge among patients in dexmedetomidine group. It is unlikely that this was a result of an overdose of dexmedetomidine as the drug infusion was titrated to a predefined endpoint (Ramsay score of 3) and the dosage used was in keeping with standard practice.

References

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