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# Comparison between Effects of Midazolam and Dexmedetomidine as Sedative in Elective Caesarean Section under Spinal Anaesthesia

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## Abstract

This randomized clinical trial compares midazolam and dexmedetomidine in terms of onset and recovery of sedation, haemodynamic effects, respiratory effects, and adverse effects of both the drugs in elective Caesarian section under spinal anaesthesia. The study included 60 ASA grade-I patients between age 20- and 40-years undergoing elective Caesarean sections under subarachnoid anaesthesia, from January 2022 to June 2022. Patients were randomly allocated to one of the two groups: midazolam group (Group-I, n=30), who received midazolam in a single dose of 0.10mg/kg and Dexmedetomidine group (Group-II, n=30), who received dexmedetomidine in a single dose of 2mcg/kg. Spinal anaesthesia was conducted by injecting a hyperbaric solution of 0.5% bupivacaine 3ml through a 25G spinal needle at L3-4 level. All parameters were documented at 5-minute intervals until arousal of the patient. The onset of sedation i.e., time from IV (intravenous) injection of Midazolam or Dexmedetomidine to closure of eye lids (OAA/S score of 3) and the arousal time from sedation i.e., time from closing of the eye lids to OAA/S score of 5 (patient is awake clinically) were noted. Any complication during operation was documented. The patient's satisfaction with the sedation was assessed by the 5-point 'Likert verbal rating scale'. There was no significant difference of mean blood pressure and mean heart rate between the two groups at different time intervals (P>0.05). Time of onset of sedation was significantly delayed in dexmedetomidine group (P<0.05). Duration of sedation was comparable between the two groups (P>0.05). Incidence of peroperative complications were comparable between the two groups (P>0.05). Haemodynamic effects and adverse effects of two drugs were comparable. Therefore, it is recommended that either midazolam or dexmedetomidine can be used for sedation in single dose technique during subarachnoid block for Caesarean section.

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## Introduction

Spinal (Subarachnoid) anaesthesia is the method of choice for elective Caesarean section. It allows mother to be involved in the child's delivery but also exposes them to awareness related stress during the procedure. The stress intensity is higher in women undergoing a Caesarean section compared with women delivering spontaneously.[1] The use of pharmacological sedation after extraction of the foetus by Caesarean section under Subarachnoid anaesthesia is useful in some patients e.g. those presenting with high stress.

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Enhanced stress can result from poor foetal health after delivery, discomfort associated with immobilization on the operating table, chills that accompany anatethesia, nausea, vomiting and environment of operating room.[2]

Sedation is a valuable tool to provide general comfort for the patient. Oversedation may jeopardize the safety of the patient. While levels of sedation progress in a dose response continuum, it is not always possible to predict precisely how an individual patient will respond to a particular dose.[3] Oversedation may be associated with untoward effect of respiratory and cardiovascular depression resulting in higher chances of airway instrumentation and hypotension leading to a prolonged stay in the post anaesthetic care unit, entailing increased burden on staff, bed availability and associated costs.[4,5] Thus judicious use of sedation can make surgeries under spinal anaesthesia more comfortable for the patient, the surgeon and the anaesthesiologist. As a result, it can increase the patient's acceptance of regional anaesthetic technique.[6]

Midazolam, a short acting benzodiazepine, is frequently used as a sedative during procedures under spinal anaesthesia. It has a property of rapid onset and offset of action after intravenous (IV) injection. It has the advantage of producing anxiolysis and amnesia.[7] Dexmedetomidine is a highly selective α2 agonist that has sedative, analgesic, anxiolytic and amnesic effects without a significant respiratory depression. It displays a dose dependent blood pressure response. It has a sympatholytic effect through decreasing the concentration of norepinephrine which in turn decreases the heart rate and blood pressure.[8]

There are a good number of studies regarding the use of sedative agents during regional anaesthesia, but it is scarce in case of Caesarian section where a pregnant woman has anatomical and physiological changes from its non-pregnant counterpart. Our study aims to find out the time of onset and recovery from sedation with midazolam and dexmedetomidine, to evaluate and compare the properties of both drugs in terms of haemodynamic effects, respiratory effects, and adverse effects, as adjuncts to spinal anaesthesia.

## Methods

This randomized clinical trial included 60 ASA (American Society of Anesthesiologists) grade-I patients between age 20-40 years undergoing elective Caesarean sections under Subarachnoid anaesthesia during the period January 2022 to June 2022 in the Combined Military Hospital (CMH), Chattogram, Bangladesh. The exclusion criteria were positive history of drug allergies, patients suffering from heart disease, hypertension, diabetes, spinal deformity, neurological disorder, any bleeding disorder and unwilling to accept sedation during spinal anaesthesia. Patients were randomly allocated to one of the two groups: midazolam group (Group-I, n=30), who received Midazolam in a single dose of 0.10mg/kg and dexmedetomidine group (Group-II, n=30), who received Dexmedetomidine in a single dose of 2mcg/kg (over 10min).

A written informed consent was taken from all patients. They were fasted for a minimum of 6 hours before surgery. No preoperative opioid or prophylactic antiemetic were given. No other preoperative medication was allowed. All patients

were monitored with electrocardiograph, non-invasive blood pressure and pulse oximeter monitor.

Baseline vital parameters were recorded. Preloading was done with 300ml Ringer lactate within 5-10 minutes prior to block. Spinal anaesthesia was conducted by injecting a hyperbaric solution of 0.5% bupivacaine 3ml through a 25G spinal needle at L3-4 level. After spinal block, patients were placed on the operating table in horizontal position. Sedation with Midazolam and Dexmedetomidine was administered after extraction of the foetus. Oxygen inhalation by ventimask was given when $SpO_2$ (saturation percentage of arterial oxygen) came down below 90% and vasopressor was given if MAP (mean arterial pressure) decreased beyond 20% of baseline. MAP was measured continually at 5 min interval and heart rate (HR), $SpO_2$ were monitored throughout the surgery. All parameters were documented at 5 min intervals until arousal of the patient. The onset of sedation i.e., time from iv injection of midazolam or dexmedetomidine to closure of eye lids (OAA/S score 3) and the arousal time from sedation i.e., time from closing of the eye lids to OAA/S (Observer's Assessment of Alertness/ Sedation) score of 5 (patient is awake clinically) were noted.[9]

Any complication during operation was documented. The patient's satisfaction with the sedation was assessed by the 5-point 'Likert verbal rating scale' with some questions like 'where will you put your experience with this sedation on the scale?' in a language which the patient understands, at a point of time when the patient had a mental state suitable for communication.

Data were analysed using Statistical Package for the Social Science (SPSS) for Windows version 12.0 (SPSS Inc., Chicago, IL, USA). Independent 't' test, paired 't' test and Chi-square test were applied. Data were expressed in mean±SD. P-value <0.05 was considered statistically significant.

Ethical approval was obtained from the Ethics Review Board of the Combined Military Hospital (CMH), Chattogram, Bangladesh.

## Results

60 respondents (30 in each group) were included in this randomized clinical trial. Group-I (Midazolam group) and Group-II (Dexmedetomidine group) were found to be comparable in respect of age, weight, duration of surgery (time from surgical incision to surgical closure) (Table-I).

**Table-I:** Demographic data of the patients (N=60)

| Variables | Group I (n=30) | Group II (n=30) | P value |
|---|---|---|---|
| Age (years) | 30.23±5.3 | 29.10±4.6 | 0.654 |
| Weight (kg) | 66.51±9.8 | 67.53±8.7 | 0.741 |
| Duration of surgery (min) | 51.66±4.5 | 50.65±3.4 | 0.743 |

Values are expressed in mean±SD

There was no significant difference in Mean arterial pressure between the two groups before Spinal anaesthesia (baseline), after spinal block, before sedative drug administration and after drug administration (Table-II). Mean heart rate between the two groups were not significantly different before Spinal anaesthesia (baseline), after spinal block, before sedative drug administration and after drug administration (Table-III).

**Table-II:** Comparison of mean arterial pressure (mmHg) at various time intervals (N=60)

| Time Intervals | Group I (n=30) | Group II (n=30) | P value |
|---|---|---|---|
| Before Anaesthesia (baseline) | 79.1±7.54 | 80.2±6.88 | 0.664 |
| After Spinal block | 76.3±5.59 | 75.7±5.43 | 0.751 |
| Before drug administration | 73.7±7.41 | 74.1±6.42 | 0.723 |
| After drug administration | 72.1±8.41 | 71.7±8.39 | 0.748 |

Values are expressed in mean±SD

**Table-III:** Comparison of mean heart rate (bpm) at various time intervals (N=60)

| Time Intervals | Group I (n=30) | Group II (n=30) | P value |
|---|---|---|---|
| Before Anaesthesia (baseline) | 79.3±9.69 | 78.4±10.39 | 0.718 |
| After Spinal block | 86.3±11.17 | 88.1±10.51 | 0.688 |
| Before drug administration | 81.6±11.71 | 78.6±9.84 | 0.661 |
| After drug administration | 86.5±10.07 | 81.5±11.18 | 0.543 |

Values are expressed in mean±SD

Onset of sedation was delayed in Dexmedetomidine group (P<0.05). Duration of sedation was comparable between the two groups (P>0.05). Percentage of patients satisfied with sedation was comparable between the two groups (P>0.488) (Table-IV). Incidence of complications were comparable between the two groups (Table-V).

**Table-IV:** Comparison of sedation characteristics (N=60)

| Variables | Group I (n=30) | Group II (n=30) | P value |
|---|---|---|---|
| Time required for onset of sedation (eye closure) (min.) | 1.67±0.51 | 6.54±2.51 | 0.046 |
| Arousal time from sedation in min (OAA/S score of 5) | 25.3±6.37 | 26.2±5.38 | 0.758 |
| Satisfaction with sedation (good) | 26 (86.66%) | 24 (80%) | 0.688 |

Values are expressed in mean±SD

**Table-V:** Incidence of complications between two groups (N=60)

| Variables | Group I (n=30) | Group II (n=30) | P value |
|---|---|---|---|
| Nausea and Vomiting | 6 (20%) | 4(13.33%) | 0.488 |
| Chills | 4 (13.33%) | 2 (6.66%) | 0.389 |
| Restlessness | 3 (10%) | 4(13.33%) | 0.688 |
| Pain in arm | 1 (3.33%) | 3 (10%) | 0.301 |

## Discussion

Pregnant women undergoing elective Caesarean sections under Subarachnoid anaesthesia are often anxious about the unpleasant experience associated with awareness during surgery. After being informed about the possible use of hypnotics after baby extraction, the patients usually more eagerly accept this suggested method of anaesthesia.[2]

The most widely used technique for administering sedation in regional anaesthesia is the intermittent bolus dose technique. This technique has been shown to be associated with peaks and troughs in plasma concentration producing significant side effects and delayed recovery.[10] Continuous infusions have been proved to produce, lesser side effects, faster recovery, easy controllability over the desired depth of sedation but requires some especial equipment e.g., syringe pump, BIS monitor etc., which is expensive and not available everywhere. Moreover, it needs more expertise like interpretation of EEG.[11]

When using sedative medication during regional anaesthesia technique, the anaesthesiologist attempts to titrate the drug to optimize patient comfort while maintaining cardiorespiratory stability and intact protective reflexes. The assessment of depth of sedation has been traditionally performed by observing clinical parameters such as appearance, response to voice, and pain on surgical stimulation. These parameters are qualitative and assessment of response to voice requires patient stimulation, which may itself alter depth of sedation.[12]

We chose the OAA/S scale for assessment of sedation over other scales as it was easier to use, comprehensive and inclusive of parameters such as facial expression and eyelid ptosis in addition to speech and responsiveness, which are not there in other sedation scales.[12] Similarly the OAA/S scale has been shown to have an inter-rater agreement that varies between 85% and 96% depending on the level of sedation, which is higher than most of the other scales used for the same purpose, making it the most suitable choice if precise assessment of sedation is required.[11] Benzodiazepines via GABAergic receptors produce anxiolysis as well as sedation and anterograde amnesia. Midazolam is the most commonly used drug. It has rapid onset and short duration of action which enables its easy dose titration. Benzodiazepines at higher doses leas to cardiorespiratory depression, so require monitoring.[13] Dexmedetomidine, a potent and highly selective α2-adrenoceptor agonist, has been safely used to sedate patients under regional anaesthesia. It induces potent sedation through its action on the locus coeruleus, the predominant brainstem nucleus involved in sleep regulation and respiratory control. Compared to traditional sedatives patients treated with dexmedetomidine have better arousability and cooperation, minimal respiratory depression, and better postoperative cognitive function. Dexmedetomidine is usually given initially as a bolus, followed by continuous infusion. Single dose dexmedetomidine can also provide adequate sedation during short procedures under spinal anaesthesia.[14]

Jo *et al*. conducted a randomized trial on 116 adult patients, who were assigned to receive either midazolam (n=58) or dexmedetomidine (n=58) during spinal anaesthesia. Systolic, diastolic, and mean arterial pressure; heart rate, peripheral oxygen saturation, and bispectral index scores were recorded during surgery, and Ramsay sedation scores and postanaesthesia care unit (PACU) stay were monitored. Hypotension occurred more frequently in the midazolam group (P<0.001) and bradycardia occurred more frequently in the dexmedetomidine group (P<0.001). Mean Ramsay sedation score was significantly lower in the dexmedetomidine group after arrival in the PACU (P=0.025) and

PACU stay was significantly longer in the dexmedetomidine group (P=0.003). They concluded that BIS guided dexmedetomidine sedation can attenuate intraoperative hypotension, but induces more bradycardia, prolongs PACU stay, and delays recovery from sedation in patients during and after spinal anaesthesia as compared with midazolam sedation.[15] In our study, haemodynamic effects of the two drugs were comparable. There was no incidence of bradycardia with dexmedetomidine. Recovery from sedation was comparable between the two groups. Duration of PACU stay was not included in our study.

Ali Hassan conducted a randomized clinical trial to compare two techniques of moderate sedation for patients undergoing ERCP, using either dexmedetomidine or ketofol as regards haemodynamic, sedation, pain, respiratory effect, recovery time, patients' and endocopists' satisfaction, and complications during and after the procedure. Fifty patients were randomly allocated in one of two groups; dexmedetomidine group D (n=25) received 1mcg/kg IV bolus over 10 min followed by 0.5mcg/kg/h or ketamine-propofol (ketofol) group KP (n=25) received 1mg/kg iv bolus followed by 50mcg/kg/min. After loading dose, HR and MAP were significantly lower in group D as compared with group KP (P<0.05). HR was significantly lower in group D during the recovery (P<0.05). No significant difference between both groups as regards time to achieve RSS, MAS, FPS and total dose of rescue sedation. Personnel restraint was significantly lower in group KP (8% versus 20%) than in group D. Endoscopists' satisfaction was significantly higher in group KP than D group (92% and 80%) respectively. He concluded that ketofol (1:1) provided better haemodynamic stability than dexmedetomidine and standard alternative to it in moderate sedation during ERCP.[8] In our study, we compared the effects between midazolam and dexmedetomidine. Dexmedetomidine showed stable haemodynamic effects.

Esmaoglu *et al.* compared the effectiveness of midazolam and dexmedetomidine for the sedation of eclampsia patients admitted to intensive care unit. Forty women with eclampsia requiring termination of pregnancy by caesarean delivery were randomized into two groups of 20 to receive either midazolam or dexmedetomidine. The midazolam group received a loading dose of 0.05mg/kg followed by an infusion of 0.1mg/kg/h. The dexmedetomidine group loading dose was 1mcg/kg over 20 minutes, followed by continuous infusion at 0.7 mcg/kg/h. Heart rate, blood pressure, Ramsay sedation score, antihypertensive need, convulsion fits, and duration in ICU were monitored and recorded all through the ICU stay. Dexmedetomidine markedly reduced heart rate for the first 24 hours (P<0.05) compared with midazolam, but there was no difference at 48 and 72 hours. Mean arterial blood pressures were similar in the 2 groups (P>0.05), although in the dexmedetomidine group, it was lower at 5, 6, 12 and 24 hours compared with the first 4 hours (P<0.05). Moreover, fewer patients given dexmedetomidine required nitroglycerine and nitroprusside (P<0.05). The duration of ICU stay was less in the dexmedetomidine group, 45.5 hours (range, 15-118 hours), than in the midazolam group, 83 hours (15-312hours). So, they concluded that dexmedetomidine sedation in eclampsia patients is effective in reducing the

demand for antihypertensive medicine and duration of ICU stay.[16] In our study, dexmedetomidine has stable haemodynamic effects. There was no incidence of bradycardia with dexmedetomidine. Patient selection criteria in our study was different from the above study.

However, we had some limitations. The intervention was not placebo controlled and blinded to neither clinicians nor patients. Additionally, group sizes were small. Consequently, the clinical relevance remains undetermined and further studies are necessary to confirm potential benefits between the two commonly used sedatives.

## Conclusion

Although onset of sedation was significantly delayed in dexmedetomidine group, there was no significant difference in duration of sedation between midazolam and dexmedetomidine in single dose technique for sedation during Caesarean section. Haemodynamic effects and adverse effects of two drugs were comparable. Therefore, it is recommended that either midazolam or dexmedetomidine can be used for sedation during spinal anesthesia for Caesarean section.

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