Original Article

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Clonazepam Versus Diazepam as Sedative in Elective Caesarean Section Under Spinal Anaesthesia

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ABSTRACT

Background: *Regional anaesthesia has become an important anaesthetic technique now a days. The use of spinal anaesthesia is often limited by the unwillingness of patients to remain awake during surgery. Pharmacologically induced tranquility improves acceptance of regional technique. This study compares Clonazepam and Diazepam in terms of onset and recovery of sedation, haemodynamic effects and adverse effects of both the drugs during elective caesarian section under spinal anaesthesia.*

Materials and methods: *This randomized clinical trial included 60 ASA (American Society of Anaesthesiologists) grade I patients between age 20-40 years undergoing elective Caesarean sections under spinal anaesthesia during the period of January 2022 to June 2022. Patients were randomly allocated to one of two groups: Clonazepam group (Group C, n=30), who received Clonazepam in a single dose of 0.015mg/kg and Diazepam group (Group D, n=30), who received Diazepam in a single dose of 0.15mg/kg.*

Results: *There was no significant difference of mean blood pressure and mean heart rate between the two groups (p>0.05). Time of onset and duration of sedation was comparable between the two groups (p value 0.759 and 0.652 respectively). Percentage of patient satisfaction was comparable between the two groups(80% vs 86.66%, p value 0.841). Incidence of pain in arm during drug administration was significantly more in Diazepam group (10% vs 100%, p<0.001).*

Conclusion: *Both Clonazepam and Diazepam have satisfactory haemodynamic stability and sedation characteristic in single dose technique during spinal anaesthesia for caesarean section.*

Key words: Clonazepam; Diazepam; Sedation; Spinal anaesthesia.

Introduction

Spinal 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 underwent a caesarean section compared with women delivering spontaneously.[1] The use of pharmacological sedation after extraction of the foetus by caesarean section under spinal anaesthesia is useful in some patients e.g. those presenting with high stress. 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. Over sedation 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] Over sedation 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]

Clonazepam is a long acting benzodiazepine which is primarily used to control seizure attack. It is highly lipophilic, allowing rapid onset of effects in the brain. It is also used as premedicant drug to relieve anxiety preoperatively. However, there is still little information

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on the efficacy of Clonazepam as sedative in patients undergoing surgery.[7,8] Diazepam is a long acting benzodiazepine, insoluble in water, so diluted in propylene glycol solution. It has onset of action up to 30 min. and elimination half life of 20-100 hours as a result of its biphasic elimination. It can be administered Intravenously (IV) Intramuscularly (IM) and orally. It is one of the cheapest benzodiazepines available in market. It has sedative, amnesic and anticonvulsant properties.[7]

The aim of this study was to compare the time of onset and recovery from sedation with Clonazepam and Diazepam, to evaluate and compare the properties of both drugs in terms of haemodynamics and adverse effects, as adjuncts to spinal anaesthesia.

Materials and methods

This randomized clinical trial included 60 ASA (American Society of Anesthesiologists) grade I patients between age 20-40 years underwent elective caesarean sections under Subarachnoid anaesthesia during the period of January 2022 to June 2022. 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 two groups: Clonazepam group (Group C, n=30) who received Clonazepam in a single dose of 0.015mg/kg and Diazepam group (Group D, n=30) who received Diazepam in a single dose of 0.15mg/kg. Written informed consent were taken from all participants. Ethical approval was obtained from proper authority. 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 Clonazepam or Diazepam was administered after extraction of the foetus. O_2 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 Clonazepam or Diazepam 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 (Observer's Assessment of Alertness/ Sedation) 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' 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.

Observer's Assessment of Alertness/ Sedation (OAA/S) Scale

Category	Observation	Score Level
Responsiveness	Responds readily to name spoken in normal tone	5
	Lethargic response to name spoken in normal tone	4
	Responds only after name is called loudly and/or repeatedly	3
	Responds only after mild prodding or shaking	2
	Does not respond to mild prodding or shaking	1
Speech	Normal	5
	Mild slowing or thickening	4
	Slurring or prominent slowing	3
	Few recognizable words	2
Facial expression	Normal	5
	Mild relaxation	4
	Marked relaxation (Slack jaw)	3
Eyes	Clear, no ptosis	5
	Glazed, or mild ptosis (Less than half the eye)	4
	Glazed and marked ptosis (Half of the eye or more)	3

Figure 1 Likert Scale for satisfaction

Data were analysed using Statistical Package for the Social Science (SPSS) for Windows (Version 12.0, SPSS Inc,. Chicago, IL, USA). Independent 't' test was used for age, weight, duration of surgery, time for recovery, heart rate, mean arterial pressure and SpO_2 at

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various time intervals. Chi square test was applied for adverse effects. Paired 't' test was applied for intra-group variation in heart rate and mean arterial pressure. Data were expressed in mean, SD and percentage. $p<0.05$ was taken to be of statistically significant.

Results

60 respondents (30 in each group) were included in this randomized clinical trial. The Group C (Clonazepam group) and Group D (Diazepam group) were found to be comparable in respect of age, weight, duration of surgery (Time from surgical incision to surgical closure) (Table I).

There was no significant difference in Mean Arterial Pressure (MAP) between the two groups before Spinal anaesthesia (Baseline) after spinal block and before sedative drug administration. Fall in mean arterial pressure was observed inboth the groups after drug administration but that was not statistically significant (Table II).

There was no significant difference in mean heart rate between the two groups before spinal anaesthesia (Baseline) after spinal block and before sedative drug administration. Rise in mean heart rate was observed in both groups after drug administration but that was not statistically significant (Table III). Mean values of SpO_2 remained stable throughout the surgical procedure in both the groups, with no statistically significant aberrations ($p>0.5$).

Time of onset of sedation and duration of sedation was comparable between the two groups (p value 0.759 and 0.652 respectively). Patient satisfaction with sedation was comparable between the two groups (p value 0.841)(Table IV).

Incidence of pain in arm during drug administration was significantly more in Diazepam group ($p <0.001$). Other complications were comparable between the two groups (Table V).

Table I Demographic data of the patients under study (n=60)

Attributes	Group C (n=30)	Group D (n=30)	p value
Age (Years)	28.53±5.4	29.49±5.4	0.764
Weight (Kg)	65.53±10.8	67.39±10.8	0.643
Duration of surgery (min)	50.66±5.6	49.66±5.6	0.684

Values are expressed in mean±SD
SD- Standard Deviation.

Table II Comparison of MAP (mmHg) in study groups at various time intervals (n=60)

Time Interval (Minutes)	Group C (n=30)	Group D (n=30)	p value
Before Anaesthesia (Baseline)	82.1±8.54	83.3±7.54	0.741
After Spinal block	75.8±6.47	77.7±5.47	0.739
Before drug administration	76.4±6.41	74.4±7.39	0.643
After drug administration	73.3±8.41	72.7±6.43	0.639

Values are expressed in mean±SD
SD- Standard Deviation.

Table III Comparison of mean heart rate (bpm) in study groups at various time intervals (n=60)

Time Interval (Minutes)	Group C (n=30)	Group D (n=30)	p value
Before Anaesthesia (Baseline)	78.9±12.69	77.9±11.89	0.843
After Spinal block	87.4±11.97	85.3±11.93	0.651
Before drug administration	75.6±12.71	77.6±11.86	0.541
After drug administration	81.5±10.08	83.4±9.87	0.683

Values are expressed in mean±SD
SD- Standard Deviation.

Table IV Comparison of sedation characteristics in study groups (n=60)

Responses	Group C (n=30)	Group D (n=30)	p value
Time required for onset of sedation (Eye closure) (min)	1.81±0.51	1.39±0.41	0.759
Arousal time from sedation in min (OAA/S score of 5)	38.3±6.37	45.3±5.32	0.652
Satisfaction with sedation (Good)	24 (80%)	26 (86.66%)	0.841

Values are expressed in mean±SD
SD- Standard Deviation.

Table V Incidence of complications in study groups (n=60)

Complication	Group C (n=30)	Group D (n=30)	p value
Nausea and Vomiting	4 (13.33%)	5 (16.7%)	0.757
Chills	2 (6.66%)	3 (10%)	0.526
Restlessness	4 (13.33%)	4 (13.33%)	0.966
Pain in arm	3 (10%)	30 (100%)	<0.001

Discussion

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.[9] Continuous infusions have been proved to produce, lesser side effects, faster recovery, easy controllability over the desired depth of sedation but requires some especial equipments e.g. syringe pump, BIS monitor etc, which is expensive and not available everywhere. Moreover, it needs more expertise like interpretation of EEG.[10]

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When using sedative medication during regional anaesthesia technique, the anaesthesiologist attempts to titrate the drug to optimize patient comfort while maintaning 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.[11]

The OAA/S scale was selected 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]

Benzodiazepines via GABAergic receptors produce anxiolysis as well as sedation and anterograde amnesia. Clonazepam is a benzodiazepine drug with anxiolytic, anticonvulsant, and muscle relaxant properties. It has long elimination half-life (19-60 hrs). It does not have any active metabolite and may be kept at ambient temperature.[13]

Zanette et al. conducted a randomized clinical trial in which eighty eight patients underwent oral surgery were randomly sedated with equipotent cumulative doses of diazepam and midazolam, up to a maximum dose of 8 mg, 4 mg respectively. Patient's tranquility was assessed after every dose, using a visual analogue score to ten points and the sedation was evaluated as mild, moderate or deep. Blood pressure, heart rate and SpO_2 were also recorded. Psychomotor conditions, by Newman test and the incidence of amnesia and patient's satisfaction, by telephone interview, were both evaluated. The average scores of tranquility were higher after diazepam. Patients treated with diazepam experienced a higher incidence of mild sedation, patients treated with midazolam a higher incidence of moderate and deep sedation. In midazolam group, blood pressure, heart rate and SpO_2 were lower. Postoperative recovery was similar in the two groups. After midazolam, patients experienced greater amnesia for local anaesthesia and drowsiness. Satisfaction was high with both treatments. The recovery and satisfaction were comparable in the two groups.[14] In This study, it was not measured the level of sedation, because it would cause interruption of sedation. There was no significant difference between the blood pressure changes, heart rate and saturation between Clonazepam and Diazepam groups. Patient's satisfaction was comparable between the two groups. Recovery characteristics were not included in the study.

Agbakwuru et al. carried out a prospective observational study on 50 adult patients who underwent hydrocelectomy using intramuscular diazepam sedation and spermatic cord block with 0.5% plane xylocaine. 4% of the patients were converted to general anaesthesia. All patients except one preferred to have future surgery under such local anaesthesia and sedation.[15] In our study, we compared the sedative characteristics between Clonazepam and Diazepam during spinal anaesthesia which showed no significant difference between them.

Sachdeva et al. conducted a prospective randomized single blind study on the effect of sedation during upper gastrointestinal endoscoly. The patients were randomized to receive either placebo or sedation with midazolam or diazepam before endoscopy. The endoscopist and the observer recording patient's/ physician's responses were blinded to the drugs administered. The patient's discomfort and the physician's comfort during the procedure were recorded on a visual analogue scale rating from 1-10 within 10 minutes of the procedure by an independent observer. There was no statistical difference in the discomfort experienced by the patients during endoscopy when sedation was used ($p=0.0754$). Only 20% patients undergoing endoscopic procedures complained of significant discomfort, but there was no difference in the ones undergoing intervention with or without sedation ($p<0.854$). The physicians were more comfortable in performing endoscopic procedure in sedated patients, however, the difference between patients in diazepam group and midazolam group was not statistically significant ($p< 0.0461$). They concluded that both diazepam and midazolam fared equally well in increasing physician's comfort ($p<0.617$) and there was no difference in the patient's discomfort with regard to the sedative used (Midazolam or diazepam).[16] In this study, placebo was not included and patient's satisfaction was measured by 'Likert like Scale'. Surgeon's satisfaction was not included in study. Patients satisfaction with sedation was comparable between Clonazepam group and Diazepam group.

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 sedatives.

Conclusion

The study showed that both Clonazepam and Diazepam have satisfactory haemodynamic stability and sedation characteristic in single dose technique during spinal

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anaesthesia for caesarean section. Incidence of pain in arm during drug administration was significantly more in Diazepam.

Recommendation

It is recommended that Clonazepam is a better choice than Diazepam for sedation in single dose technique during spinal block for caesarean section.

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Disclosure

All the authors declared no competing interests.

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