

Comparison between Propofol, Midazolam and Clonidine for Bis-Guided Sedation during Spinal Anaesthesia

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Abstract: Background: regional anaesthesia has several advantages over general anaesthesia including spontaneous ventilation, retained upper airway reflexes, early post-operative ambulation and lower cost. Hence it is the preferred mode of anaesthesia whenever possible. Among the disadvantages are absence of anxiolysis and intolerance in case of prolonged surgeries. Several drugs like propofol, midazolam and α_2 agonists as clonidine can be used as a sedative agents to overcome some disadvantages of spinal anaesthesia. **Aim of the Work:** was to find out the time for onset and recovery from sedation with these drugs, using BIS as a standard measure of depth of sedation and to evaluate and compare the properties of propofol, midazolam and clonidine as regard haemodynamics, side effects and dosage requirement as adjuvants to spinal anaesthesia. **Patients and Methods:** this study was done from March, 2018 to November 2018 at Al-Zahraa university hospital. After obtaining local medical ethics committee approval and written informed consents from all the patients in the study, sixty (60) patients American Society of Anaesthesiologists (ASA) physical status classes I and II, with age between 20-50 years of both sex undergoing lower abdominal, perineal and lower limb surgeries which were anticipated to complete within 1 hour. **Results:** the present study demonstrated that, propofol has advantage of providing faster onset of sedation, rapid clear headed recovery and more sedative efficacy than midazolam and clonidine. The three drugs of study have negligible side effects and hemodynamics changes. **Conclusion:** propofol was found to be superior to midazolam and clonidine with respect to depth of sedation, onset and clear headed recovery from sedation with negligible side effects.

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1. Introduction

In the recent days regional techniques have come to take an upper hand in anaesthesia over general anaesthesia owing to its certain, often underestimated advantages such as lesser chances of airway compromise and aspiration, facilitation of postoperative analgesia, inherent benefit in some preexisting medical conditions and avoidance of operation theatre pollution⁽¹⁾.

In spite several advantages of regional anaesthesia over general anaesthesia, it has disadvantages. Among this disadvantages are absence of anxiolysis, irritability and inadequacy in case of prolonged surgeries⁽²⁾.

Conscious sedation is being widely used in various diagnostic, surgical and therapeutic procedures. It is a controlled state of pharmacological depression of consciousness enabling treatment to be carried out and communication is maintained throughout the period of sedation besides maintaining protective reflexes. It avoids the adverse psychological and physiological effects of stress. It reduces anxiety in frightened and agitated patients⁽³⁾.

Despite the established record of safety of conscious sedation, problems may have occurred, these include hypoventilation, apnoea, airway obstruction and cardiopulmonary impairment. Appropriate agents provide safe and effective sedation and ensure greatest margin of safety⁽⁴⁾.

Monitoring of various aspects of regional anaesthesia are important as in general anaesthesia. Amongst monitoring equipment available to the modern anaesthetist, Bispectral Index (BIS) is perhaps the latest and the best suited tool. Besides providing an idea about the hypnotic state of the patient, it also enables titration of anaesthetic agents so as to avoid adverse effects as awareness due to inappropriate dosage as well as unwanted effects of overdosage⁽⁵⁾.

We performed a study comparing sedative effects of propofol, midazolam and clonidine using BIS in spinal anaesthesia.

Aim of the Work

The aim of our study was to find out the time for onset and recovery from sedation with these drugs, using BIS as a standard measure of depth of sedation and to evaluate and compare the properties of propofol, midazolam and clonidine as regard

haemodynamics, side effects and dosage requirement as adjuvants to spinal anaesthesia.

2. Patients and Methods

This study was done from March, 2018 to November 2018 at Al-Zahraa university hospital.

After obtaining local medical ethics committee approval and written informed consents from all the patients in the study, sixty (60) patients American Society of Anaesthesiologists (ASA) physical status classes I and II, with age between 20-50 years of both sex undergoing lower abdominal, perineal and lower limb surgeries which were anticipated to complete within 1 hour.

Exclusion criteria:

- History of allergy to the local anaesthetic drug or to the study drugs.
- History of cardiac disease, hypertension.
- Psychological disease.
- Spinal deformities, contraindication to spinal anesthesia such as coagulation defects infection at the puncture site, pre-existing neurological deficits and hemodynamic instability.

The patients were divided into 3 equal groups, 20 patients for each group.

- **Midazolam group (Group M)** were received midazolam 0.1% infusion starting with initial rate 0.05 mg/kg/h, then the dose titrated to maintain a BIS of 65-80.

- **Propofol group (Group P)** were received Propofol 1% infusion starting with initial rate 6mg/kg/h, then the dose titrated to maintain a BIS of 65-80.

- **Clonidine group (Group C)** were received Clonidine infusion Starting with initial rate 1mcg/kg/h, then the dose titrated to maintain a BIS of 65-80.

In the pre-operative room, an intravenous wide bore cannula (18G) was inserted and infusion started with Ringer's lactate at 10ml/kg over 30 min, another intravenous cannula (20G) was obtained for infusion of the study drugs. While shifting the patient to the operating room, the anaesthetic machine, resuscitating drugs and BIS device with its sensors were checked. Syringe pump filled with drugs that used in the study were prepared and kept ready for use.

Standard monitoring (non-invasive blood pressure, electrocardiography and pulse oximetry) was attached and the baseline parameters (mean arterial pressure, heart rate and peripheral arterial oxygen saturation were recorded).

The patients were divided into three groups:

Group M: were received midazolam 0.1% infusion manufactured by Sunny pharmaceutical Company, Germany (5mg/1ml was diluted to 50 ml of

normal saline.9%), starting with dose 0.05 mg/kg/h, then the dose titrated to maintain a BIS of 65-80.

Group P: were received Propofol 1% infusion manufactured by Fresenius Kabi Austria Company, Germany (400 mg/40 ml). Starting with dose 6mg/kg/h, then the dose titrated to maintain a BIS of 65-80.

Group C: were received Clonidine infusion manufactured by Sunny pharmaceutical Company, Germany (150mcg/1ml was diluted to 50ml of normal saline.9%) Starting with initial rate 1mcg/kg/h, then the dose titrated to maintain a BIS of 65-80.

Under strict aseptic technique, lumbar puncture was performed at L4-L5 or L3 -L4 or spinal interspace, in sitting position, through a standard midline approach using a 25-G Quincke spinal needle. Hyperbaric bupivacaine (0.5%) 15 mg to 20 mg was injected intrathecally. Sensory block at T10 and peak sensory block was noted using sterile pin prick method. Bromage scale for time of onset of motor block was assessed. level of sensory block less than T10 or motor block less than Bromage 3 were not included in the study as general anesthesia was administered to them, also patients who needed vasopressor or atropine were excluded from the study.

BIS sensors were connected to the forehead of the patient after wiping the skin by alcohol swap. Drugs used in the study were infused through a syringe pump.

Intraoperative heart rate, non-invasive blood pressure, SpO₂ were recorded every 5 minutes. BIS score and Modified Ramsay sedation scale were used for intra-operative assessment of sedation.

Oxygen supplementation via oxygen mask was given when Spo₂ decreased below 95%.

Measuring Parameters:

1. Demographic data: Age, sex, weight, ASA, duration and type of surgery.
2. Heart rate, mean arterial blood pressure, spo₂ were recorded every 5 minutes till end of the surgery.
3. Time to reach required level of sedation (BIS 65-80).
4. Time taken for recovery (BIS>90 was taken as a recovery parameter).
5. Ramsay sedation score.
6. Side effects:-Nausea and Vomiting.
 - Airway affection.
 - Pain in site of infusion.
 - Restlessness.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. Also qualitative variables were presented as number and

percentages. The p-value was considered significant as the following: P-value > 0.05: Non significant

(NS), p-value < 0.05: Significant (S), p-value < 0.01: Highly significant (HS).

3. Results

Table 1: Demographic data in three groups.

		Propofol group	Midazolam group	Clonidine group	Test value	P-value	Sig.
Age (yrs)	Mean±SD	38.45 ± 10.06	34.85 ± 10.85	33.15 ± 9.22	1.446•	0.244	NS
	Range	20 – 50	20 – 50	20 – 50			
Sex	Females	7 (35.0%)	4 (20.0%)	8 (40.0%)	2.003*	0.367	NS
	Males	13 (65.0%)	16 (80.0%)	12 (60.0%)			
BW (kg)	Mean±SD	69.07 ± 6.57	72.12 ± 4.57	73.02 ± 5.34	2.779•	0.071	NS
	Range	55 – 79	66 – 80	64 – 80			
Medical history ASA	I	10 (50.0%)	15 (75.0%)	14 (70.0%)	3.077*	0.215	NS
	II	10 (50.0%)	5 (25.0%)	6 (30.0%)			
Duration of surgery (h)	Mean±SD	1.52 ± 0.42	1.52 ± 0.42	1.57 ± 0.38	0.126•	0.882	NS
	Range	1 – 2.3	1 – 2.3	1 – 2.3			

There was no statistically significant difference between three groups regarding Age, sex, body weight, ASA physically status and surgical duration (P-Value > 0.05) as shown in (table 7).

Table 2: Comparison between three groups regarding Spo2.

SPO2		Propofol group	Midazolam group	Clonidine group	Test value	P-value	Sig.
0min (Baseline parameter)	Mean±SD	99.9 ± 0.31	99.60 ± 0.50	99.60 ± 0.50	3.000	0.058	NS
	Range	99 – 100	99 – 100	99 – 100			
5min	Mean±SD	99.05 ± 0.83	99.60 ± 0.50	99.60 ± 0.50	5.098	0.009	HS
	Range	98 – 100	99 – 100	99 – 100			
10min	Mean±SD	98.1 ± 1.33	99.80 ± 0.41	99.80 ± 0.41	27.318	0.000	HS
	Range	96 – 100	99 – 100	99 – 100			
15min	Mean±SD	97.7 ± 1.03	99.60 ± 0.50	99.60 ± 0.50	46.034	0.000	HS
	Range	96 – 99	99 – 100	99 – 100			
20min	Mean±SD	97.55 ± 0.61	99.60 ± 0.50	99.60 ± 0.50	96.492	0.000	HS
	Range	97 – 99	99 – 100	99 – 100			
25min	Mean±SD	97.35 ± 0.88	99.60 ± 0.50	99.60 ± 0.50	79.658	0.000	HS
	Range	96 – 99	99 – 100	99 – 100			
30min	Mean±SD	97.95 ± 0.61	99.40 ± 0.50	99.40 ± 0.50	48.275	0.000	HS
	Range	97 – 99	99 – 100	99 – 100			
35min	Mean±SD	97.25 ± 1.02	99.40 ± 0.50	99.40 ± 0.50	59.848	0.000	HS
	Range	96 – 99	99 – 100	99 – 100			
40min	Mean±SD	97.5 ± 0.83	99.40 ± 0.50	99.40 ± 0.50	60.699	0.000	HS
	Range	97 – 99	99 – 100	99 – 100			
45min	Mean±SD	97.85 ± 0.93	99.40 ± 0.50	99.40 ± 0.50	34.912	0.000	HS
	Range	96 – 99	99 – 100	99 – 100			
50min	Mean±SD	98.4 ± 1.10	99.40 ± 0.50	99.40 ± 0.50	11.728	0.000	HS
	Range	96 – 99	99 – 100	99 – 100			
55min	Mean±SD	98.15 ± 0.93	99.20 ± 0.41	99.20 ± 0.41	18.255	0.000	HS
	Range	97 – 100	99 – 100	99 – 100			
60min	Mean±SD	99.2 ± 0.70	99.40 ± 0.50	99.40 ± 0.50	0.809	0.451	NS
	Range	98 – 100	99 – 100	99 – 100			

According to oxygen saturation (Spo₂): There was high statistical difference in Spo₂ between P group and group M, C as propofol show decrease in spo₂ up to 96% (P-Value >0.01) as shown in (table 11).

Table 3: Comparison between three groups regarding time to reach required level of sedation and time taken for recovery.

		Propofol group	Midazolam group	Clonidine group	Test value	P-value	Sig.
Time to reach required level of sedation (min). (BIS:65-80)	Mean±SD	4.81 ± 0.52	12.50 ± 1.93	14.20 ± 1.74	214.153•	0.000	HS
	Range	4 – 5.7	10 – 15	12 – 17			
Time taken for recovery (min) (BIS<90)	Mean±SD	2.28 ± 0.68	10.20 ± 1.88	1.98 ± 0.76	284.986•	0.000	HS
	Range	1 – 3	7 – 13	1 – 3			

According to time reaching required level of sedation (BIS 65-80) and time taken for recovery (BIS<90):

There was high statistical difference between group P and group M, C (P-value< 0.01) as shown in table 12. The mean time to reach required level of sedation in group P was (4.81 ± 0.52 min) which was

about 7.7 minutes later than in group M (12.50 ± 1.93min) and about 9 minutes later than in group C (14.20 ± 1.74min). Also the mean time taken for recovery in group C was (1.98 ± 0.76 min) which was earlier than in group P (2.28 ± 0.6 min) and group M (10.20 ± 1.88min).

Table 4: Comparison of three groups regarding Ramsay score.

		Propofol group	Midazolam group	Clonidine group	Test value	P-value	Sig.
Ramsay score	Mean±SD	3.90 ± 0.72	2.65 ± 0.49	2.25 ± 0.44	46.660•	0.000	HS
	Range	3 – 5	2 – 3	2 – 3			

According to Ramsay score: There was high statistical difference between group P and group M, C (P-value< 0.01) as shown in table 13, as Ramsay score of group P was ranging from 3-5 in comparison to group M and C which was ranging from 2-3.

Table 5: Comparison of three groups as regard side effects.

Side effects		Propofol group	Midazolam group	Clonidine group	Test value	P-value	Sig.
Nausea-vomiting	no	20 (100.0%)	20 (100.0%)	20 (100.0%)	NA	NA	NS
Airway affection	no	20 (100.0%)	20 (100.0%)	20 (100.0%)	NA	NA	NS
Restlessness	No	18 (90%)	20 (100.0%)	20 (100.0%)	4.138	0.126	NS
	Yes	2 (10%)	0 (0%)	0 (0%)			
Pain in arm	No	17 (85%)	20 (100.0%)	20 (100.0%)	6.316	0.043	S
	Yes	3 (15%)	0 (0%)	0 (0%)			

According to side effects: There was no statistically difference in three groups (P-Value > 0.05) as shown in (table 14) regarding nausea, vomiting and airway affection. Two patients in group P was complained of restlessness and three patients in same groups complained of pain in arm at site of injection as shown in table 14.

4. Discussion

The operating room is an anxiety provoking environment. So supplemental sedative intravenous agents are often required to allay fear and anxiety in

patients subjected to spinal anaesthesia. Sedation is a valuable tool to make surgery under regional anesthesia convenient for the patient, the anaesthetist and the surgeon ⁽⁶⁾.

Conscious sedation is a minimally depressed level of consciousness that maintain airway stability and to respond appropriately to physical stimulation and verbal commands. ⁽⁷⁾.

Intravenous bolus dose technique has been shown to be associated with peaks and frequent changes in plasma concentrations producing significant side effects and delayed recovery.

Continuous infusions have been proved to produce lesser side effects, faster recovery and easy control to reach required depth of sedation⁽⁸⁾.

The objective of the study was to compare sedative, hemodynamic and recovery characteristics of propofol, midazolam and clonidine given in continuous infusion for conscious sedation in patients undergoing surgery under spinal anaesthesia.

In our study, the dose of sedative drugs needed to reach required level of sedation (BIS:65-80) was 2mg/kg/h in propofol as in a dose of 6 mg/kg/h a BIS score reached 40 in all patients so the dose titrated up to 2mg/kg/h, 0.05mg/kg/h for midazolam and 1mcg/kg/h in clonidine. Similar doses used in other studies as **Bagchi et al.**⁽⁹⁾ and **Khurana et al.**⁽¹⁰⁾.

As regard time needed to reach required level of sedation (BIS 65-80), the current study shows that required sedation level achieved much faster by propofol infusion (4.81 ± 0.52 min) as compared to midazolam (12.50 ± 1.93 min) and clonidine (14.20 ± 1.74 min) and the difference in the findings was seen to be highly significant ($p < 0.01$). Regarding time needed for recovery (BIS > 90) our study shows that midazolam (10.20 ± 1.88 min) was slowest drug in comparison to clonidine (1.98 ± 0.76 min) and propofol (2.28 ± 0.6 min) and the difference in the findings was statistically highly significant ($p < 0.01$).

Several studies as **Bhosle et al.**⁽¹¹⁾, **Bagchi et al.**⁽⁹⁾; **Patki and Shelgaonkar**⁽¹²⁾, **Khurana et al.**⁽¹⁰⁾ and **Al-Khayat et al.**⁽¹³⁾ also confirm that propofol has advantage of providing faster onset of sedation and rapid clear headed recovery over midazolam.

As regard hemodynamics Propofol, midazolam and clonidine are known to inhibit sympathetic activity and decrease systemic vascular resistance resulting in some amount of bradycardia and hypotension⁽¹⁴⁾.

In the present study we observed that, these drugs in sedative infusion doses did not significantly alter mean heart rate or mean arterial pressure throughout the procedure. This could be possibly attributed to the fact that they were administered in subanaesthetic doses.

Our findings were comparable to those of some other studies as **Bhosle et al.**⁽¹¹⁾, **Lordan et al.**⁽¹⁵⁾ and **Khurana et al.**⁽¹⁰⁾ who found that subsanaesthetic sedative doses of midazolam and propofol do not alter baseline cardiovascular variables.

A study against us conducted by **Bagchi et al.**⁽⁹⁾ this study revealed that propofol infusion cause hypotension and bradycardia more than midazolam infusion, but said the cause may due to cephalic spread of spinal anaesthesia which excluded from our study from the beginning.

As regard spo₂, the study drugs are known to depress respiratory function when given in inducing doses which dose not used in current study. In our study, neither midazolam nor clonidine infusion cause any significant alteration in mean spo₂ throughout the procedure, in propofol infusion spo₂ significant decreased up to 96% but patients didn't need oxygen supplementation. A study carried by **Bhosle et al.**⁽¹¹⁾ also confirmed this result.

Regarding side effects, there were negligible side effects caused by study drugs. It was found that in the propofol group only 2 patients complained of restlessness and 3 patients in the same group complained of pain in site of injection especially in using dose 6 mg/kg/h before titration which is significant. Similar results found in some other studies as **Bhosle et al.**⁽¹¹⁾ and **Khurana et al.**⁽¹⁰⁾.

Conclusion

When conscious sedation is considered during spinal anaesthesia, propofol, midazolam and clonidine offer good sedation and good cardiorespiratory stability.

From our study: Propofol was found to be superior to midazolam and clonidine with respect to depth of sedation, onset and clear headed recovery from sedation with negligible side effects.

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