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Comparative Evaluation of Efficacy and Safety of Intravenous Propofol and Dexmedetomidine for Intraoperative Sedation during Subarachnoid block: A Prospective Study

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Abstract

Aims: **C**omparing Propofol and Dexmedetomidine to assess the relative safety and efficacy in achieving adequate intraoperative sedation (Ramsay Sedation Score of 3–4) and cardiorespiratory safety in patients undergoing abdominal hysterectomy under subarachnoid block. *Setting and Design:* Department of Anesthesiology pain & Palliative Medicine, ESI PGISMR and Hospital, Manicktala (Tertiary Care Government Hospital located in Kolkata, WB, India) Operation theatres, Postanesthesia Care Unit, Gynecology & Maternity Ward. *Study Design*: Uni-centric prospective double blinded comparative *Statistical analysis used*: With Shapiro-Wilk test and Chi-square test *Materials and Methods:* Forty female participants between 18 and 65 years of age were divided into two groups *via* systematic random sampling. After administering subarachnoid block with 15 milligrams of 0.5% hyperbaric bupivacaine, bolus IV Dexmedetomidine (Group D, n = 20) or Propofol (Group P, n = 20) was started. All patients were monitored. Dexmedetomidine and Propofol infusions were discontinued at the end of surgery and the patients were transferred to the Postanesthasia Care Unit (PACU). The modified Aldrete scoring system was used to assess the readiness for shifting the patients to the postsurgical wards. *Results:* Both the groups had comparable demographics and basal values of heart rate, blood pressure, respiratory rate, ASA physical status, duration of infusion, depth of sedation, incidence of hypotension, bradycardia, over-sedation, but Group P had higher incidence of transient respiratory depression which were easily manageable.

Keywords: Propofol; Dexmedetomidine; Intraoperative Sedation; Procedural Sedation; Spinal Anesthesia.

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Introduction

Subarachnoid block (spinal anesthesia) is one of the commonest anesthetic techniques worldwide owing to its simplicity and predictability. It is established that underlying stress, anxiety, unfamiliar environment of the operating room and more importantly intraoperative awareness can lead to short-term and long-term undesirable consequences.[1] Despite, procedural sedation being recognized to have paramount importance while a patient is operated under regional anesthesia, it is less frequently used by anesthesiologists

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during subarachnoid block, probably because of a valid concern regarding patient safety.[2] The key deterring factor seems to arise from the potential cardiorespiratory compromise that might occur with the use of conventional procedural sedatives above and over subarachnoid block which bears its own set of overlapping physiological changes.[3] The concern seems to be even more profound if the center is under equipped or remotely located. Propofol is by far the most commonly used agent for procedural sedation in India, the routine usage during subarachnoid block seems to be limited in more equipped centers.[4] This study was designed to investigate the cardiorespiratory safety of conventionally used agents in procedural sedation *viz*. Propofol and comparing its effects with relatively a novel agent Dexmedetomidine, which is considered to have a better cardiorespiratory safety profile.[5-7] For this study to be reproducible in remote locations, the primary outcome was measured on easily noticeable clinical parameters and basic hemodynamic monitoring. Although, Bispectral Index (BIS) was used during this study to objectively assess the depth of sedation in parallel with clinical scales (Ramsay Sedation Scale, RSS), has not been accounted to be the primary determinant of therapeutic target.[8,9] The goal of this study was to assess safety, choosing the right agent and estimating the mandatory duration of postoperative observation with procedural sedation during subarachnoid block. *The principle objectives were*: (a) to investigate if intraoperative sedation during subarachnoid block could be safe in ASA I and ASA II patients with Propofol and Dexmedetomidine; and (b) to compare the efficacy, safety and advantages of one agent over the other.

Materials and Methods

This study planned in accordance with the principles of Helsinki declaration. After obtaining the approval from the Institutional Ethical Committee on 11.1.2014, forty patients admitted for elective abdominal hysterectomy were divided into Two Groups Group "P" and Group "D" *via* computer-generated systematic randomization. This study was performed with all safety measures, equipment and backup systems ready. Informed consent by the participants in own language was taken, and they could opt out anytime. Group P was designed to receive Propofol and Group D with Dexmedetomidine for the purpose of procedural sedation.

Study area: Department of Anesthesiology pain & Palliative Medicine, Name of the Institute ESI PGISMR and Hospital, Manicktala (Tertiary Care Government Hospital located in Kolkata, WB, India) Operation theatres, Postanesthesia Care Unit, Gynecology & Maternity Ward.

Study population: Women undergoing abdominal hysterectomy under Subarachnoid block.

Age group: 18–65 years of age.

Study design: Uni-centric prospective double blinded comparative study.

Method of randomization: Computer-generated Systematic Random Sampling.

A windows-based random number generator program called "Random Number Generator 1.3" (under Freeware license by 2×D Soft) was used to randomly arrange a set of 40 discrete serials numbers. Correspondingly 40 closed paper vouchers of identical size was created with those numbers. From the resultant roster, odd ones in the sequence were labelled "Group P"; and even ones as "Group D". Group P (n = 20) were to receive Propofol and Group D (n = 20) received Dexmedetomidine for intraoperative procedural sedation.

Inclusion criteria

1. Patients of between 18 and 65 years old,
2. Patients with ASA I–II,
3. Patients undergoing Abdominal Hysterectomy under subarachnoid block.

Exclusion criteria

1. Patients with Hemodynamic Instability,
2. Known Hypersensitivity Reactions to the Drugs,
3. Contraindications to Subarachnoid Block,
4. Obstetric Patients,
5. Uncontrolled Hypertension/Diabetes,
6. Substance Abuse/Addiction (Opium Products/Alcohol),
7. Patients on Sedative Medications,
8. Diagnosed Neurological/Psychiatric Illness, Electrolyte Imbalance, Documented Metabolic, Cardiac, Renal, Hepatic illness.

The depth of sedation was monitored by the Ramsay Sedation Score (RSS) along with monitoring of vital signs:

Ramsay Sedation Scale (Score):

1. Patient anxious, agitated, or restless,
2. Patient cooperative, oriented, and tranquil alert,
3. Patient responds to commands,
4. Asleep, but with brisk response to light glabellar tap or loud auditory stimulus,
5. Asleep, sluggish response to light glabellar tap or loud auditory stimulus,
6. Asleep, no response.

The final preanesthetic checkup was done one day before operation. Information that were recorded for each cases were age, gender (all female, in our case), height and weight of the patients, presence of concomitant diseases, history for drug use and smoking and ASA classification. If she was found fully eligible for the study, an informed consent was taken. The patient was also educated on how to respond for assessment of RSS Scoring. The patients were kept on preoperative fasting as per ASA guidelines.[10] Premedication was given in form of 5 mg Midazolam tablets 60 minutes before the schedule in the preoperative area. An intravenous cannulation was done with 18G cannula on the nondominant forearm. As per institutional protocol, intravenous hydration with 10 ml/kg/hr Ringer's lactate was started 30 min before performing subarachnoid block. The study serial number was retrieved by randomly opening a voucher previously generated and the patient was tagged. The corresponding grouping information for that serial was retrieved from the Roster by the personnel who would be administering the drugs. The grouping information was kept strictly confidential from both the patient and the assessor. The patients were not labelled with any grouping information. The infusion pump was kept facing against the assessor and was controlled by the drug administrator only. Patients were monitored with noninvasive arterial blood pressure, electrocardiogram, heart rate, pulse oximetry and bispectral index.

After local infiltration, subarachnoid block was performed in sitting position, *via* L4-L5 interspace using a 25-gauge Quincke's needle (B. Braun Medical, Melsungen, Germany) while maintaining strict aseptic techniques with 12.5 milligrams of 0.5% hyperbaric bupivacaine (ANAWIN HEAVY 0.5%, NEON Inc, Mumbai, India). The patients were finally positioned supine. After confirming the onset of subarachnoid block bilaterally to the T4 level, bolus IV Dexmedetomidine for Group D and Propofol for Group P was started.

Patients in Group P received Propofol (NEOROF®, NEON Inc., Mumbai, India) at a dose of 1 mg/kg as the loading dose over 1 minute and then infusion was started at a rate of 50 mcg/kg/min and continued till the end of surgery. Group D received Dexmedetomidine (DEXTOMED®, NEON Inc., Mumbai, India) infusion at a dose of 1 μg/kg for the first 10 min and 0.5 μg/kg/h throughout the surgery. Both groups simultaneously received Ringer's Lactate at a rate of 10 mL/kg/h for the first hour and continued at a rate of 5 mL/kg/h. The time at which the RSS score comes between 3 and 4 was considered the time of start of sedation. BIS was noted as a secondary objective measurement. Patients were given with IV midazolam 0.5 mg as 'rescue sedation'; doses repeated until the patient exhibited a RSS score ≥ 3. The infusions were temporarily paused if there were RSS Score of 6 or BIS < 40 at any point of time, until RSS is ≤ 5 or BIS > 40. The systolic mean blood pressure, heart rate, peripheral oxygen saturation, respiratory rate and level of sedation were recorded every 5 min intervals after Dexmedetomidine or Propofol infusion being started, and also at the Postanesthesia Care Unit (PACU). Dexmedetomidine and Propofol infusions were discontinued at the end of surgery and the patients were transferred to the PACU. The modified Aldrete scoring system was used to assess recovery from anesthesia (score ≥ 9).[11] Patients were discharged from PACU to the respective Gynecology wards, after two hours of continuous uneventful observation. Stay in the PACU were extended if significant distress was experienced by the patient, in form of nausea, vomiting, respiratory distress, rebound sedation, headache etc. or the observed parameters indicate inadequate recovery, shown as in (Table 1).

Table 1: Time from Start of Infusion to Start of Sedation

	Group	N	Mean	Std. Deviation	Std. Error Mean	
Time of Onset of Sedation	D	20	11.5000	2.85620	.63867	$p < 0.001$
	P	20	6.7500	2.93571	.65645	

Working Definitions: Hypotension was defined as systolic blood pressure of less than 90 mm Hg or decrease of 30% from baseline and were treated with a bolus administration 6 mg of intravenous Mephentermine.[12] Bradycardia was defined as heart rate < 50 beats/min and treated with 0.6 mg of intravenous atropine.[13] Respiratory depression was defined, as respiratory rate < 8/min, or peripheral oxygen saturation declining below 90%.[14] The patients were managed by a quick evaluation to detect tongue fall back, or lack of respiratory drive and managed either by airway manipulation like jaw thrust or bag-mask ventilation. Emergency airway cart and standby ventilators were kept ready for all cases. Over sedation was defined as RSS Score of 6 or BIS < 40.

Data Analysis: All data were expressed as mean ± standard deviation. Parametric demographic data were analyzed using one-way analysis of variance (ANOVA). Sphericity of data was assessed with Shapiro-Wilk test. Nonparametric data were compared using Chi-square test. The study groups were compared by independent sample (unpaired sample) '*t*' test (with Bonferroni correction) for arterial blood pressure, heart rate, respiratory rate and peripheral oxygen saturation. RSS Score was compared using Friedman's test. *p* - values of < 0.05 considered significant. Statistical analysis has been performed using SPSS software (version 23.0; IBM Inc., Chicago, IL, USA, 2015). Results were cross-checked with GraphPad Prism version 6.01 for Windows OS (GraphPad Software Inc., California, USA.

Results

Sample characteristics, in terms of age in years (P: 54.1 ± 4.78; D: 55.55 ± 3.09), ASA classification, BMI (P: 25.44 ± 4.45; D: 25.17 ± 4.03) were found similar. Basal values of SBP in mm Hg (P: 134.05 ± 9.62; D: 136.95 ± 9.07), Respiratory Rate: (P: 22.3 ± 3.47; D: 23.4 ± 2.68) were also similar. There was an observed difference in the time of onset of sedation: (P: 6.75 ± 2.94; D: 11.5 ± 2.86). There was an early incision time in Group P (P: 8.95 ± 3.24; D: 13.3 ± 2.13; *p* - value 0.032). Shown in Table 2, duration of infusion in both groups were similar (P: 59.55 ± 8.27; D: 56.95 ± 7.09), and difference in the duration of sedation were nonsignificant (P:62.25 ± 8.19; D:59 ± 8.68). None needed rescue sedation, shown in Table 3. There was a statistically significant difference in the duration of sedation after stopping infusion at the end of surgery,shown as in Table 4. Time to reach Modified Aldrete Score of 9, were comparable in both groups. Hypotension was observed in 10 [P: 6 (60%) D: 4 (40%)], bradycardia was observed in 4 [1 (25%) in Group P and 3 (75%) in Group D]. Over sedation & Respiratory Depression were noted in 2 ($p = 0.147$) and 4 ($p = 0.035$) cases respectively, all belonged to Group P. Out of them, 3 were managed with Jaw thrust and bag-mask ventilation, 1 patients needed LMA insertion. Incidence of Postoperative Nausea and Vomiting (PoNV) observed in 6 with 3 cases in each group. Change in mean BP following the initial bolus doses in both group were not significant. RSS Scores had no significant difference in first 90 minutes, except there was a difference in first 10 minutes of infusion, with Group P having a lower rank.

Discussion

This study was unique in terms of comparing both the agents in patients undergoing operations of equivalent operative-stress (abdominal hysterectomy) under subarachnoid block to eliminate an important confounding factor of variable levels of the surgical stimuli, gender predisposition (the study population consisted exclusively female), age.

The depth of sedation was comparable in both the groups. But, the time of onset of sedation was significantly shorter in Group P, which is probably attributable pharmacokinetics of Propofol and the initial rate of infusion to induce sedation (1 minute in Propofol, whereas 10 minutes in Dexmedetomidine). Possibly, because of the same reasons, Group P showed an initial spike in RSS at 5–10 minutes postinitiation, compared to Group D, who experienced a spike in RSS score at 25–30 minutes postinitiation. Consequently, there was a scope for early incision time in Group P, saving costly resources.

The incidence of hypotension and bradycardia was comparable in both groups. The incidence of respiratory depression was more in Group P, which tend to occur immediately after the bolus infusion. But, no incidence of apnea during maintenance dose of Propofol was observed, more importantly, they were fewer in comparison than that was being perceived from earlier case reports.[15] Postoperatively, subjects in Group D experienced lower heart rate and BP, possibly because of waning spinal, supplemented by residual analgesic effects of Dexmedetomidine, or may be attributed to early elimination of Propofol.

Procedural sedation during subarachnoid block with either of the agent in the studied dosage was

safe, when continuous monitoring was done. Early detection of adverse situations like hypotension and bradycardia needed careful vigilance, but were manageable with commonly available drugs like Atropine and Mephentermine. Respiratory depression, observed with Propofol were managed with simple airway manipulations/interventions. Over sedation was found to be a relatively rare occurrence with either of the agent at the studied dosage, and Ramsay Sedation Scale (RSS) was sufficient to diagnose over sedation in absence of monitors like BIS. In both cases of over sedation, RSS was found to be comparatively early predictor to detect over sedation than BIS (BIS reading was above 40 in both cases). Postoperative monitoring in PACU for a period of two hours was found sufficient in all of the study subjects, before shifting to ward.

Conclusion

Choosing the right agent for procedural sedation should be guided by patient's profile. No agent could be found superior over the other in the context of quality of sedation, at the studied dosages sedation during subarachnoid block can be generally safe, with careful clinical vigilance, and

Table 2: Duration of Infusion

Parameters	Group	N	Mean	Std. Deviation	Std. Error	Mean
Duration of Infusion	D	20	56.9500	7.08947	1.58525	$p = 0.292$
	P	20	59.5500	8.26836	1.84886	

Table 3: Duration of Sedation after Stopping Infusion

Parameters	Group	N	Mean	Std. Deviation	Std. Error	Mean
Duration of Sedation after Stopping Infusion	D	20	13.5500	3.39466	0.75907	$p = 0.001$
	P	20	9.4500	3.60519	0.80614	

Table 4: Time for Modified Alderete Score of 9 after Stopping Infusion

Parameters	Group	N	Mean	Std. Deviation	Std. Error	Mean
Time for Modified Alderete Score of 9 after Stopping Infusion	D	20	11.5000	3.28473	0.73449	$p = 0.218$
	P	20	12.7500	3.02403	0.67619	

Table 5: Friedman Test: RSS Score

Ranks					
Group	**Time Mean**	**Rank Time**	**Group**	**Mean Rank**	***p* Value (from ANOVA)**
D	0	0	P	3.08	
	5	5		8.73	0.004
	10	10		13.00	0.001
	15	15		13.88	0.531
	20	20		11.65	0.345
	25	25		11.93	0.268
	30	30		11.90	0.076
	35	35		12.45	0.886
	40	40		13.18	0.048
	45	45		11.33	0.020
	50	50		12.13	0.406
	55	55		9.70	0.679
	60	60		7.55	0.347
	100	100		3.23	0.813
	110	110		3.10	0.757
	115	115		3.10	0.316
	120	120		3.10	0.561

basic hemodynamic monitoring. To draw a definite conclusion on the feasibility of its application in remote and underprivileged areas, wider population-based multicentric study is necessary.

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