Original Article

Comparative Evaluation of Efficacy and Safety of Dexmedetomidine in patients with and without Beta blockers for Vitreo-retinal surgery

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ABSTRACT

Background: Dexmedetomidine is an alpha-2 adrenoceptor agonist that has sedative and analgesic effects with no respiratory depression. There was a need to verify the safety and efficacy of intravenous Dexmedetomidine in patients on therapeutic doses of beta blockers posted for vitreo-retinal surgeries under peribulbar block.

Material and methods: A prospective, comparative cohort study with 35 patients on beta blockers in Group B and 35 patients without beta blockers in Group N, over one year was included in the study. All patients received Dexmedetomidine 0.25µg/Kg loading dose over 10 min followed by maintenance dose of 0.25µg/Kg/hr, titrated to attain 3-4 Ramsay sedation score.. Following fifteen minutes of Dexmedetomidine IV infusion, peribulbar anaesthesia was administered. The vital parameters monitored were heart rate, blood pressure (BP) (systolic, diastolic, mean), respiratory rate, nasal end-tidal carbon di-oxide, SpO_2 and level of sedation.

Results: There was no statistically significant fall in the heart rate or BP in patients on beta blockers (Group B) compared to patients without beta blockers (Group N). No respiratory depression was observed.

Conclusion: Dexmedetomidine is a safe and efficacious sedative in the patients on beta blockers when loading dose (0.25µg/Kg over 10mins) and maintenance dose (0.25µg/Kg/hr) is titrated through close monitoring of vital parameters.

Key Words: Dexmedetomidine, peribulbar block, intravenous Sedation, beta blocker, vitreo-retinal surgeries.

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Introduction

In ophthalmic surgical procedures, regional anaesthesia is preferred over general anaesthesia owing to quicker patient rehabilitation and better analgesia provided post operatively. But, injection of local anaesthesia and lying down still for prolonged period of time can cause pain, discomfort and phobic attack. Sedatives with stable haemodynamics can alleviate these problems. Alpha-2 adrenergic agonists have both sedative and analgesic properties. It augments the local anaesthetic effects by altering trans membrane potential and ion conductance at locus ceruleus in the brainstem. Also, it produces stable haemodynamics and decreased oxygen demand due to enhanced sympatho-adrenal stability.

Dexmedetomidine ($C_{13}H_{16}N_2$) is an highly selective alpha-2 adreno-receptor agonist with sedative, analgesic and anxiolytic properties with minimal respiratory depression.[1,2] α-1 to α-2 ratio of 1:1600 makes it as a highly selective α-2 agonist compared to clonidine, thus reducing the unwanted side effects involving α-1 receptors. Dexmedetomidine-induced biomimetic sleep states benefit patients by eliminating drug-induced neurocognitive dysfunction that result from unintended drug action in sensory, memory encoding, and cognitive processing circuits. Early (Dexmedetomidine-induced) and late (Dexmedetomidine-associated) N2, N3 sleep stages are biomimetic.[3]

It is increasingly being used as a sedative for monitored anaesthesia care (MAC) due to its analgesic properties,"conscious sedation," and lack of respiratory depression.[4] It also provides better patient satisfaction, less opioid requirements, and less respiratory depression than placebo rescued with midazolam and fentanyl.[5] Peribulbar block (PBB) with Dexmedetomidine provide conscious sedation, decreases pain during performance of block,[6] lowers intraocular pressure,[7] prevents hypertensive response to anxiety, improves patient's comfort[8] and thus provide potentially better operating conditions for the surgeon. The usual dose for procedural sedation is 1 μg/ kg, followed by an infusion of 0.2 μg/kg/hr. Its onset of action is less than 5 minutes and the peak effect occurs within 15 minutes. As the pharmacologic effects can be reversed by the α2-AR antagonist Atipamezole, Dexmedetomidine provides hypnotic sedation that can be reversed readily.[4]

Intraoperative bradycardia and hypotension are major concerns with the above recommended dose. But, when it is infused at a reduced loading dose of 0.25μg/Kg over 10min followed by titrated maintenance dose it provides stable hemodynamics. Avoiding narcotic analgesics reduces post-operative nausea and vomiting which is an additional benefit.[9] In the adult studies, Dexmedetomidine yielded significantly lower pain score levels compared to the other sedatives (31.25%) and significantly more patient satisfaction (68.2%).[10]

The purpose of this study was to evaluate efficacy and safety of intravenous Dexmedetomidine in patients with or without beta blockers undergoing vitreo-retinal surgeries under regional anaesthesia. Noninvasive measures of respiratory status with sufficient accuracy and reliability are preferred. Pulse oximetry is a valuable indicator of oxygenation but cannot substitute capnography as an indicator of ventilation, given oxygenation and ventilation are distinctly different physiological processes and thus require separate but complementary monitoring methods.[11] The primary aim of the study was to compare the haemodynamic parameters, respiratory parameters and the level of sedation. The secondary aim was to evaluate the role of nasal capnography ($EtCO_2$) during procedural sedation for vitreo-retinal surgeries.

Material and methods

This observational cohort study was started after approved by institutional ethics committee [IEC NO:2017/10 Dt: 15.05.2017] and clinical trial registry [CTRI/2018/08/015387]. Written informed consent was obtained from all the patients. Sample size was based on the average number of patients on beta blockers per year posted for vitreo-retinal surgeries under intravenous sedation and PBB in the last three years. Total 70 patients posted for elective vitreo-retinal surgery under intravenous sedation and PBB, over one year were included.

Patients were divided into two groups (n=35), Group B, on beta-blockers and Group N, not on beta-blockers.

Patients aged between 40 to 75 years, belonging to ASA grade 1 to 3 were included. Patients aged more than 75 years, having basal heart rate less than 50 beats per minute, severe left ventricular dysfunction (Ejection fraction <35%), hypovolemia with systolic blood pressure <90mm Hg, heart blocks, chronic renal failure and hepatic impairment, bleeding or coagulation abnormalities, psychiatric diseases and having history of allergy to the local anaesthetic or dexmedetomidine were excluded from the study.

Pre anaesthetic check-up was done and fasting of 3-4 hours was ensured. Baseline vitals (heart rate, systolic, diastolic, mean blood pressure (BP), respiratory rate) were noted and all patients received oral Alprazolam 0.25mg-0.50mg as anxiolytic premedication and oral Pantoprazole 40mg with Domperidone 30mg. Patient was shifted to operation theatre, and monitors were connected. Intravenous access was secured and maintenance fluid was started. Vitals parameters (heart rate, systolic BP, diastolic BP, mean BP, respiratory rate, SpO_2, nasal $EtCO_2$ at zero minute was noted before starting Dexmedetomidine IV sedation.

Dexmedetomidine concentration 5µg/ml (dilution 100µg in 20 ml normal saline) loaded in a 20ml syringe and delivered through a syringe pump.

All patients received loading does of Dexmedetomidine 0.25µg/Kg over 10 min followed by maintenance dose of 0.25µg/Kg/hr, titrated to attain 3-4 Ramsay sedation score.8 Supplemental oxygen 3-4 liters per min via nasal cannula was given to all patients, till the end of the surgery. Following 15 mins of infusion, PBB with 8ml of local anesthetic (4 ml of 0.5% bupivacaine plus 4ml of 2% lignocaine and hyaluronidase 15 IU/ml) was given.

Patients were evaluated for motor akinesia from grade 0-2, zero [free movement], one [partial movement and 2 [no movement]. This was done for each of four recti, levator superioris and orbicularis oculi muscles. The maximum score 12, indicated total akinesia. An eye with a score less than 8 received a repeat injection with the same local anesthetic mixture (not exceeding maximum safe dose) and recorded. Vital parameters were noted every 5 minutes for the first 15 minutes and then every 15 minutes till the end of the surgery. The bed side monitoring of vital parameters continued every 30 minutes for 2 hours in the post- operative ward.

Critical values of vital parameters are shown in Table 1.

Table 1: Critical values of vital parameters

CRITICAL VALUES								
	HR (bpm)	**Blood Pressure (mmHg)**			**RR**	**$EtCO_2$**	**SpO_2**	**LOS**
		Systolic	**Diastolic**	**Mean**				
High	>100	>180	>100	>140	>30	>40	NA	>4
Low	<50	<90	<60	<60	<10	<15	<90	NA

HR – Heart rate; bpm – beats per minute

Adverse effects like bradycardia, hypotension, respiratory depression, deeper level of sedation (level >/=5) were noted and treated. Bradycardia was considered as heart rate <50bpm and managed with IV Atropine 10 mcg/Kg or IV glycopyrrolate 0.2mg in IHD patients. Hypotension was defined as SBP <80mmHg or fall of >30% from baseline and treated with foot end elevation followed by bolus IV fluid 200-300ml, if no response then IV ephedrine 6mg considered. Respiratory depression was managed with no intervention for RR>10 / min and SpO_2 > 92%. Patient was awakened and nasal oxygen increased to 4litres / min if RR was < 10 / min and /or SpO_2 <90. In persistent respiratory depression, then plan was to stop Dexmedetomidine infusion. With deeper levels of sedation (level >/=5) maintenance dose was titrated and stopped when necessary. Dexmedetomidine infusion was stopped 10min prior to the end of the surgery (as informed by the surgeon). Post-operative pain was noted and treated with oral analgesics.

Statistical Analysis

The data was entered in Microsoft Excel and statistical analysis using Z-test. Graphs were constructed for 95% confidence interval for all parameters from baseline to 150mins. The results are considered statistically significant whenever p value is <=0.05.

Results

The data of 70 patients were collected, tabulated and analyzed. Demographic data were comparable between the groups (Table 2). The difference in heart rate between the two groups at various time intervals throughout the surgery was comparable but not statistical significance (p = 0.38). There was no statistically significant fall in the heart rate or mean BP in Group B compared to Group N, (Figure 1). P value of 0.50 at 10 mins after completing loading dose was observed. Systolic and Mean BP was comparable in both the groups, (Figure 2). At 45 mins after starting Dexmedetomidine IV infusion in Group N, diastolic BP was significantly decreased (p value=0.04), but no active intervention was required, (Figure 3). There was no statistically significant difference in respiratory rate, SpO_2 and $EtCO_2$ in both the groups.

After the loading dose of Dexmedetomidine IV infusion over 10mins, the level of sedation at 15mins was observed as Level 2 and level 4 at 60mins in both the groups, (Figure 4). There was no statistically difference in both the groups. P value was 0.5 at all-time intervals throughout the procedure.

Table 2: Demographic profile of the patients in both the Groups

Parameters		Group B (n=35)	Group N (n=35)	t-value	p value
Age (years) (mean± SD)		60.97 ± 10.15	54.57 ± 17.04	1.909	0.031
Weight (Kg) (mean±SD)		73.01 ± 12.90	66.14 ± 12.27	2.281	0.013
Gender: Male/ Female		20/15	22/13	-	-
ASA Status	ASA 1	0	2	1.456	0.073
	ASA 2	4	18	2.021	0.022
	ASA 3	31	15	4.597	P < 0.001
Mean duration of surgery (min) (mean ± SD)		105 ± 24.87	102 ± 33.11	0.469	0.320 (one-tailed) and 0.640 (two-tailed)

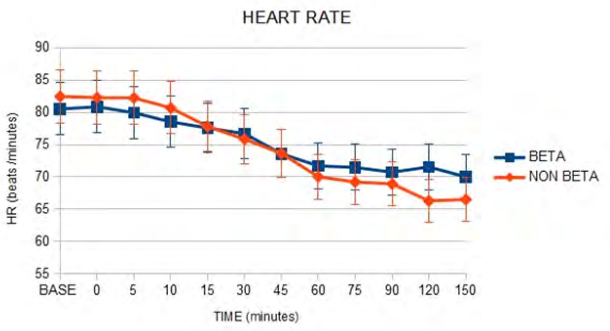

Figure 1: Heart Rate variations among the two groups at different time points

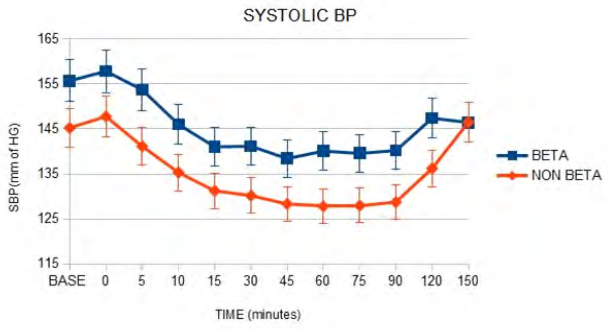

Figure 2: Systolic Blood Pressure (SBP) variations among the two groups at different time points

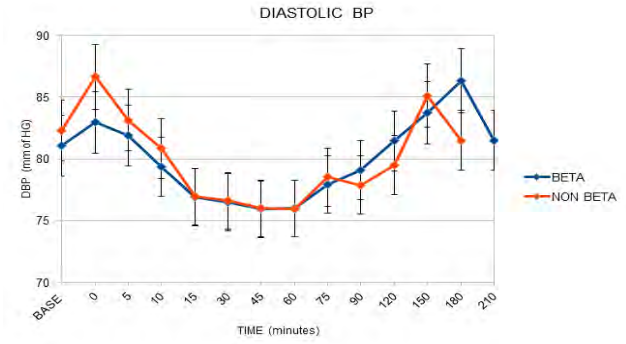

Figure 3: Diastolic Blood Pressure (DBP) variations among the two groups at different time points

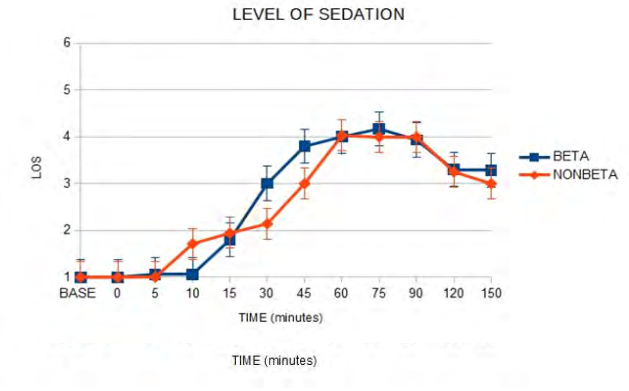

Figure 4: Level Of Sedation (LOS) variations among the two groups at different time points

Discussion

Dexmedetomidine is a highly selective alpha-2 agonist that provides anxiolysis and controlled sedation without respiratory depression. It has organ protective effects against ischemic and hypoxic injury, including cardio-protection, neuro-protection and reno-protection.[12] It produces dose dependent sedation with no respiratory depression and only modest haemodynamic effects.[13] It also has sympatholytic and anti-nociceptive effects that allow hemodynamic stability during surgical stimulation. Intravenous Dexmedetomidine exhibits linear pharmacokinetics with a rapid distribution half-life of approximately 6 minutes and a terminal elimination half-life of approximately 2 hours. It gives protection against apoptosis in retinal Ischemia/reperfusion injury in rats.[14] During pars plana vitrectomy under local anaesthesia, if need arises for cryopexy, scleral buckle or intense laser retinopexy, then sedation with Dexmedetomidine can help with good intra-operative and immediate post-operative hemodynamic control with possibility of supplemental rescue analgesia.[15]

It produces a biphasic response of the blood pressure i.e. transient hypertension (α2B - Adrenergic Receptors) followed by hypotension (α2A- Adrenergic Receptors). Bradycardia action of Dexmedetomidine is

due to the vago-mimetic action and decreased tachycardia (block of cardio acceleratory nerve). Effect of Dexmedetomidine on peripheral vasculature is vasodilation (Sympatholytic mediated) and vasoconstriction (smooth muscle cell receptor mediated). Most frequent adverse effects reported in the literature are bradycardia and hypotension mainly with loading dose of 1 μg/ kg. This can be avoided by omitting the loading dose or limiting the loading dose to 0.4 μg/ kg.[16]

Other side effects reported to occur are sinus pause/arrest, orthostatic hypotension, dry mouth. Intranasal Dexmedetomidine in elderly subjects has sedative effect, but causes a high incidence of profound and sustained hypotension irrespective of β-blocker use.[17]

Dexmedetomidine at loading dose of 0.25mcg/kg over 10 mins is a comparable, safe and effective primary sedative alternative to traditional midazolam-fentanyl combination for vitreoretinal surgery under peribulbar anaesthesia. It can be a preferred mode of sedation for better control of intraoperative hypertension. In our study there was no significant fall in the heart rate in both the groups. Atropine was not required in any patient in both the groups. There were no significant changes in the systolic blood pressure in both the groups. There was no significant fall in diastolic blood pressure in both the groups except in three patients at 45 mins in the Group B, but these three patients did not require any drug intervention and recovered by stopping the Dexmedetomidine infusion. There was no specific confounder in these three patients.

Dexmedetomidine sedation during retinal surgery improved both patient's and surgeon satisfaction without respiratory complication.[18] It is a safe and effective agent for sedation in critically ill patients.[19] In our study there was no significant change in the respiratory rate, nasal $EtCO_2$ and SpO_2 along with stable the level of sedation (Ramsay sedation score between 2-4) in both the groups.

Conclusion

Dexmedetomidine is a safe and efficacious sedative in patients on beta blockers in low doses (loading dose of 0.25μg/Kg over 10mins and maintenance dose of 0.25μg/Kg/hr) with close monitoring of vital parameters.

Financial disclosure

All authors have no financial interests to disclose.

Conflicts of Interest

There are no conflicts of interest.

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