Dexmedetomidine and Clonidine as an Adjuvant to Intrathecal Bupivacaine on Spinal Block Characteristic in Gynaecological Procedures - A Prospective Randomised Double-Blind Placebo Controlled Study

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ABSTRACT

BACKGROUND

Clonidine and dexmedetomidine are two *α-2* adrenergic receptor agonists which have been used as an adjuvant to intrathecal local anaesthetics. Both drugs act by different mechanisms and potentiate the effect of each other. The purpose of the study was to assess the efficacy and safety of adding clonidine and dexmedetomidine to intrathecal hyperbaric bupivacaine on spinal block characteristics in gynaecological procedures.

METHODS

This study was conducted as a prospective comparative, randomized, double blind, placebo-controlled trial. Based on exclusion and inclusion criteria, 90 patients were included in this study by using a computer generated randomization. Patients were randomly divided into three groups each as follows: Gr BD: 0.5 % hyperbaric bupivacaine (3.5 ml) + 3 µg preservative free dexmedetomidine (total volume of 4 ml), group BC: 0.5 % hyperbaric bupivacaine (3.5 ml) + 0.5 ml clonidine (30 µg) (total volume of 4 ml), group BN (control): 3.5 ml of 0.5 % hyperbaric bupivacaine + same volume normal saline. The spinal block characteristics, hemodynamic stability, and side effects were compared.

RESULTS

Time to reach sensory block to T10 was 2.52 ± 0.33 minutes in group BN, 1.95 ± 0.38 ms in gr BC and 1.53 ± 0.24 minutes in group BD. The span of sensory block was longer in group BD in comparison to group BC (453.76 ± 52.78 v 389.36 ± 37.4) and group BN (453.76 ± 52.78 vs. 173.33 ± 14.56). Time for rescue analgesia was 169.12 ± 21.14 minutes in group BN, 245.21 ± 32.42 minutes in group BC and 289 ± 24 minutes in group BD.

CONCLUSIONS

When *α-2* adrenergic receptor agonist is used intrathecally with bupivacaine, early motor and sensory block can be achieved along with long span of analgesia.

KEYWORDS

Bupivacaine, Dexmedetomidine, Clonidine, Spinal Anaesthesia

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BACKGROUND

Regional block is the most popular technique used for lower abdominal surgery because of its rapid onset, superior blockade, adequate analgesia, muscular relaxation, lower risk of infection, lesser failure rates, and cost-effectiveness. Various amide local anaesthetic agents are being used for regional block, out of them Bupivacaine is used most commonly.[1,2]

Bupivacaine is associated with drawbacks of shorter duration of block and less postoperative analgesia. When it is used in high concentration or accidentally administered intravascularly, it can produce cardiac arrhythmias, depression of central nervous system, respiratory depression, seizures, arrhythmia of heart and hypertension.[3,4] Adjuvants are the drugs that can not only contribute by its, own mechanism of action but also potentiate the quality of analgesia and improve the quality of block. It limits the cumulative doses of local anaesthetics so that adverse reactions are minimised.[5,6]

In last 25 years, many drugs have been used as adjuvants to local anaesthetics and have been proven clinically useful. Opioids were used commonly as intrathecal adjuvant to potentiate the local anaesthetic agent. However, post-operative respiratory depression, nausea, vomiting and urinary retention limits its use. Slowly non-opioids have replaced it.[7,8]

The *alpha 2* adrenergic blockers have been used for decades for the treatment of various cardiovascular and neurological conditions. But now these drugs are centre of interest as safe and effective adjuvant to local anaesthetic agent intrathecally[9,10]

Regarding mechanism of action of these drugs, Giovannitti JA Jr, Thoms SM, Crawford JJ, et al. has concluded that stimulation of *α-2* receptors in the dorsal horn of the spinal column inhibits nociceptive neurons and reduces the release of substance P. Zhang H, Zhou F, Li C, Kong M, Liu H, Zhang P, et al. from his study has concluded that activation of spinal α2-AR by intrathecal injection of dexmedetomidine displayed strong analgesic property via inhibition of spinal ERK1 / 2 signalling pathway.[11,12]

Clonidine and dexmedetomidine are two *α-2* adrenergic receptor agonists which have been used as an adjuvant to intrathecal local anaesthetics. There are very few studies available for comparison of *alpha 2* agonist as an adjuvant to bupivacaine. Suthar O, Sethi P, Sharma UD et al. in his study has concluded that dexmedetomidine produces an early onset of motor block and a significantly longer sensory and motor block than bupivacaine plus clonidine or bupivacaine alone.[13]

Ganesh M, Krishnamurthy D et al. has concluded that there is no difference between these two agonist when used as adjuvant.[14] Swami SS, Keniya VM, Ladi SD, Rao R et al. has concluded that dexmedetomidine enhanced the quality of block when compared with clonidine.[15] These studies have variable results so present study has been designed to assess efficacy and safety of adding clonidine and dexmedetomidine to intrathecal hyperbaric bupivacaine on spinal block characteristic in gynaecological procedures.

METHODS

This study was conducted as a prospective comparative, randomized, double blind, placebo-controlled trail from April 2017 to January 2020 in the Department of Anaesthesiology, Konaseema Institute of Medical Sciences & Research Foundation. Patients posted for elective gynaecological surgery like vaginal wall repair & vaginal hysterectomy under subarachnoid block were enrolled for this study as per these criteria. The study was started after approval from institutional ethics committee. An informed consent was taken from all patients before enrolling them for study.

Inclusion Criteria

Age 18 to 60 years
ASA I and II

Exclusion Criteria

Diabetes mellitus, spinal deformities, bleeding or clotting disorders, cardiopulmonary, renal and hepatic abnormality, peripheral neuropathy, hypersensitivity to drug and CNS disorder.

Sample Size

Based on above mentioned criteria, 90 patients were included in this study and computer-generated randomization was used, patients were randomly divided into three groups as follows:

Group BD: 3.5 ml of hyperbaric Bupivacaine (0.5 %) + 3 µg (0.5 ml) of preservative free dexmedetomidine (total volume of 4 ml)

Group BC: 3.5 ml of 0.5 % hyperbaric bupivacaine + 0.5 ml clonidine (30 µg) (total volume of 4 ml)

Group BN (control): 3.5 ml of hyperbaric Bupivacaine (0.5 %) + normal saline (0.5 ml) (total volume of 4 ml).

All patients received same preanaesthetic medication the night before surgery. All the drugs were prepared by assistant professor of anaesthesia who was not involved in this study and was handed over to the concerned anaesthesiologist for administration. Both were blinded to the study drugs.

In the preoperative room, procedure of block and visual analog scale (VAS) score was explained to each patients and routine investigations as per the requirement for preoperative evaluation and the proposed surgery was done.

In the operating room, intravenous access was achieved by 20G I.V. cannula and patients were give ringer lactate solution at 15 ml / kg volume. Standard anaesthesia monitor for vitals was attached and basal parameters like heart rate (HR), blood pressure (BP), electrocardiogram (ECG) and saturation of oxygen (SpO_2) monitoring was started. After all aseptic precautions, the total volume i.e. 4 ml of drug was injected intrathecally in subarachnoid space in lumber interspace L3 – L4. At the end of injection, time was taken to be zero min. After completion of procedure, patient was placed in supine position. Sensory testing was assessed by loss of pin prick sensation to 23G hypodermic needle

along the midclavicular line every two minutes till it reaches highest level. Surgery was allowed on achieving T10 sensory blockade level. Testing was conducted every 10 minutes till two segment regression and every 20 minutes until the recovery of S2 dermatome. The time taken to achieve a sensory level of T10 from the time of intrathecal block was taken as onset of sensory block. The time from onset to return of pin prick sensation was defined as duration of sensory block.

The motor block was evaluated by Modified bromage scale.[16] The duration from drug injection to the inability of patient to lift his extended straight leg was taken as onset time that is Bromage 3. The period of motor block was taken from time from drug injection to the ability to lift the extended leg that is Bromage 0. In the postoperative recovery room, patients were observed by anaesthesiologist who were blinded about drug used. Patients were asked to rate their pain on 11-point visual analogue scale which was repeated every 30 min for first 4 hour then hourly for next 24 hour. If VAS score reaches ≥ 4 rescue Inj. Diclofenac 1.5 mg / kg I.M. was given as rescue. From spinal administration of anaesthetic agent to the first requirement of analgesic or when VAS score reaches ≥ 4, it is called as duration of effective analgesia. Vitals included heart rate (HR), mean arterial pressure (MAP), and SPO2 were recorded at 0, 2, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, and 90 min. Patients were monitored for complications like bradycardia (heart rate below 50), tachycardia (> 20 % below baseline value), hypotension (> 20 % below baseline value) and hypertension (20 % above the normal value). Patients were asked for nausea, vomiting, drug rashes or any possible drug reactions during first 24 hours. Patient's sedation score was assessed by Ramsay sedation score.[17]

Statistical Analysis

Data was recorded in excel sheet and statistical analysis was done with software SPSS-14 version. Qualitative data was calculated as percentage and proportions and was analyzed by Chi-square test. Quantitative data was interpreted as mean ± SD and analyzed by unpaired student t-test. Analysis of variance (ANOVA) test was used to find the difference between three groups. $P < 0.05$ was considered significant.

RESULTS

All three groups were compared to each other with regard to age, American society of Anaesthesiologist (ASA) 1 and 2 and body mass index (kg / m2). Both groups were comparable to each other regarding duration of surgery.

Time taken to reach sensory level of T10 was 2.52 ± 0.33 ms in Gr BN, 1.95 ± 0.38 ms in group BC and 1.53 ± 0.24 minutes in group BD. These differences in the mean of time taken to reach sensory level of T10 between three groups was statistically significant. The time required in dexmedetomidine group was significantly early. Time taken for sensory regression of two segments was 74.46 ± 15.30 minutes in group BN, 112.96 ± 13.07 minutes in group BC and 127.63 ± 6.43 minutes in group BD. Intergroup comparison BN to BC, BN to BD and BC to BD ($P < 0.05$) was significant statistically. Duration of sensory block was significantly prolonged in group BD in comparison to group BC (453.76 ± 52.78 vs. 389.36 ± 37.4) and group BN (453.76 ± 52.78 vs. 173.33 ± 14.56). (Table 2)

Variables		Group BN	Group BC	Group BD	P-Value
Age in years		48.3 ± 9.2	49.1 ± 9.16	45.3 ± 8.35	0.238
ASA	I	16	14	12	0.385
	II	4	6	8	
BMI (kg / m2)		22.94 ± 2.4	22.46 ± 1.8	23.41 ± 2.53	0.281
Duration of surgery		79.7 ± 16.31	74.66 ± 18.15	76.36 ± 17.41	.532

Table 1. Demography of Patients in the Three Groups

Variables	Group BN	Group BC	Group BD	P Value Between the Three Groups	BN vs. BC	BN vs. BD	BC vs. BD
Time taken to achieve a sensory level of T10 (min)	2.52 ± 0.33	1.95 ± 0.38	1.53 ± 0.24	0.0001	0.0001	0.0001	0.0001
Time taken for sensory regression to two segment (min)	74.46 ± 15.30	112.96 ± 13.07	127.63 ± 6.43	0.0001	0.0001	0.0001	0.0001
Duration of sensory block (min)	173.33 ± 14.56	389.36 ± 37.4	453.76 ± 52.78	0.0001	0.0001	0.0001	0.0001

Table 2. Comparison of Sensory Block Characteristic in Groups

Variables	Group BN	Group BC	Group BD	P Value Between the Three Groups	BN vs. BC	BN vs. BD	BC vs. BD
Onset of Bromage 3 (min)	12.73 ± 1.59	8.79 ± 1.95	4.15 ± 0.58	0.0001	0.0001	0.0001	0.0001
Regression to Bromage 0 (min)	176 ± 16.54	254 ± 20.14	296 ± 54	0.0001	0.0001	0.0001	0.0001

Table 3. Comparison of Motor Block Characteristic in Groups

All three groups were significantly different with regard to time required for onset of Bromage 3 ($P < 0.05$). The onset of Bromage 3 was significantly early in group BD that is 4.15 ± 0.58 minutes and slower in group BN that is 12.73 ± 1.59 minutes.

Variables	Group BN	Group BC	Group BD	P value Between the Three Groups	BN vs. BC	BN vs. BD	BC vs. BD
Time for rescue analgesia (min)	169.12 ± 21.14	245.21 ± 32.42	289 ± 24	0.0001	0.0001	0.0001	0.0001
Total analgesic dose in 24 hrs. (min)	148.45 ± 24.12	98.60 ± 24	86.14 ± 10	0.0001	0.0001	0.0001	0.0001
VAS score	6.24 ± .48	4.89 ± .44	4.74 ± .38	0.0001	0.0001	0.0001	.244

Table 4. Comparison of Analgesic Characteristic between the Three Group

Time for rescue analgesia was 169.12 ± 21.14 minutes in group BN, 245.21 ± 32.42 minutes in group BC and 289 ± 24 minutes in group BD. This difference in mean time for rescue of analgesia between three groups was statistically

significant (P < 0.05). Highest time for rescue of analgesia was seen in group BD and lowest in group BN.

The mean of VAS score was 6.24 ± .48 in group BN, 4.89 ± .44 in group BC and 4.74 ± .38 in group BD. This difference in mean VAS score between three groups was statistically significant. Group BD has lowest VAS score and group BN has highest VAS score. But there was no significant difference in VAS score between group BC and group BD.

Variables	Group BN	Group BC	Group BD	P-Value
Bradycardia	4 (13.3 %)	2 (6.66 %)	2 (6.66 %)	
Hypotension	3 (10 %)	2 (6.66 %)	1 (3.33 %)	
Vomiting	2 (6.66 %)	3 (10 %)	1 (3.33 %)	0.89
Nausea	3 (10 %)	1 (3.33 %)	0	
Respiratory depression	1 (3.33 %)	0	0	

Table 5. Adverse Effect Comparison between the Three Groups

As per Table 5 in group BN, bradycardia was present in 13.3 % patients, hypotension was present in 10 % patients, vomiting was present in 6.66 %, nausea was present in 10 % patients and respiratory depression in 3.33 %. In group BC, 6.66 % had bradycardia, 6.66 % had hypotension, 10 % had vomiting and 3.33 % had nausea. In group BD, 6.66 % had bradycardia, 3.33 % had hypotension, and 3.33 % had vomiting. This difference in adverse effects between three groups was statistically significant.

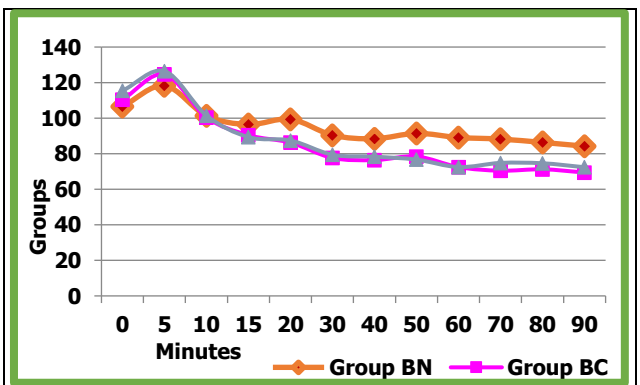

Figure 1. Comparison of Mean Arterial Pressure in the Three Groups

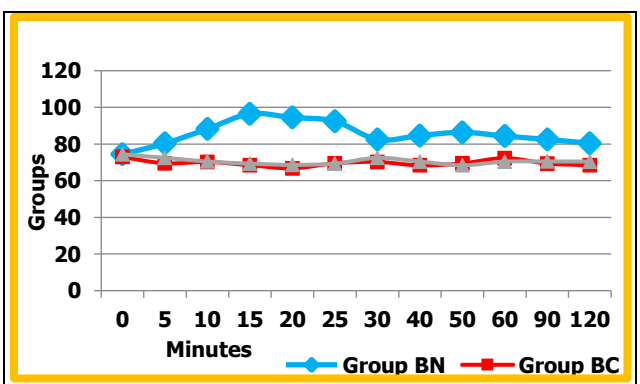

Figure 2. Comparison of Heart Rate in the Three Groups

DISCUSSION

Success of spinal block depends upon many factors like skill of anaesthetics, the choice of local anaesthetic agent and method of administration and condition of the patients.[18] An ideal local anaesthetic agent used in spinal anaesthesia should have rapid onset and longer duration of action, intense intraoperative analgesia, adequate post-operative analgesia and good cardiovascular stability. Bupivacaine is an amide local anaesthetic agent used commonly for spinal anaesthesia. It has shorter duration of analgesia and when it is used in high concentration or accidentally administered intravascularly it produces cardiac arrhythmia. Hence, adjuvants are used with these local anaesthetics to prolong the duration of anaesthesia and reduce the adverse reaction by decreasing the dose of this drugs.[19] *A2-adrenergic* agonist are new neuraxial adjuvant to bupivacaine. It acts by binding to presynaptic receptor on dorsal horn cells and inhibits release of substance P from afferent "c" fibres. Clonidine and dexmedetomidine are two *α_2-adrenergic* agonists used as adjuvant to local anaesthetics. Dexmedetomidine is more specific and selective than clonidine. Studies were available for dexmedetomidine and its intrathecal efficacy but with variable results so present study has been designed to evaluate and compare the effect of adding clonidine versus dexmedetomidine with hyperbaric 0.5 % intrathecal bupivacaine on spinal block characteristic in gynaecological procedures. Selection of the dose of dexmedetomidine (3 µg) is based on result of various studies and selection of dose of clonidine (30 µg) is calculated to be ten times as Dexmedetomidine is 8 – 10 times selective than clonidine.[9,20]

Patients enrolled in this group were divided in three groups as explained above and groups were statistically comparable to each other with respect to demographic profile and duration of surgery. This finding is supported by the work of Suthar O, Sethi P, Sharma UD et al. Ganesh M, et al.[13,14,21]

There is statistically significant difference in time taken to achieve a sensory level of T10 between the three groups. Time taken to achieve a sensory level of T-10 was faster in dexmedetomidine group than clonidine group. Time taken to achieve a sensory level of T10 was slowest in control group. This finding is supported by the study of Ganesh M, Krishnamurthy D et al. and Rahul Rajan, SN Gosavi, et al.[14, 21] Sarma J, Narayana PS, et al. and MC Soanki SL, et al. has reported that after adding adjuvant, onset of block was early but there was no statistically significant difference between dexmedetomidine and clonidine group which does not support our study.[22, 23]

Time taken for sensory regression of two segment and duration of sensory block was significantly longer in dexmedetomidine group then clonidine group. This finding corroborates with the finding of Vidhi Mahendru, et al. and MC Solanki SL, et al.[23,24] The time required to reach Bromage 3 was significantly faster in dexmedetomidine group than clonidine group but it was slowest in control group. This finding corroborates with the finding of Rahul Rajan, SN Gosavi, Vinay Dhakate, Sanjot Ninave et al.[21] Our finding was partially supported by the finding of Sarma J, Narayana PS, et al. but not supported by the study of Solanki SL, Bharti N, et al.[22,23] Time required for regression to Bromage 0 was significantly longer in dexmedetomidine group than clonidine group. This finding is supported by the work of Ganesh M, Krishnamurthy D et al. and Suthar O, Sethi P,

Sharma UD et al. but partially supported by the study of Solanki et al.[13,14,23]

We have noted that with use of 3µg dexmedetomidine as adjuvant to bupivacaine, time for rescue of analgesia was significantly prolonged and significantly reduced. 24 hour rescue analgesic requirement in comparison to 30 µg clonidine as adjuvant. This difference in mean VAS score between three groups was statistically significant. Dexmedetomidine has lowest VAS score and group control highest VAS score. But there was no significant difference in VAS score between clonidine group and dexmedetomidine group. This finding concurs with the study of Akansha Agrawal, Sanjay Agrawal, Yashwant S Payal et al. and Hemanth Kumar, VR & Krishnaveni, et al.[25,26] There was no significant difference between three groups with respect to adverse drug reaction. The bradycardia and hypotension were most common side effects reported for the use of intrathecal clonidine and dexmedetomidine which supports our study but these adverse effects were more common in control group in our study. As sample size was less significant, adverse drug reaction was not observed.[14,19]

CONCLUSIONS

When *alpha-2* receptor agonists are used as adjuvants intrathecally to hyperbaric bupivacaine, the time of onset of sensory block and onset of Bromage 3 were reduced. The time of onset was early with dexmedetomidine than clonidine. The duration of sensory and motor block was more prolonged in dexmedetomidine than clonidine. Duration of analgesia was prolonged by both adjuvants but it was longer in case of dexmedetomidine.

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