Research Paper Medical Science

A Comparison of Intrathecal Dexmedetomidine, Clonidine, and Fentanyl as Adjuvants to 0.5% Isobaric Levobupivacaine for Abdominal Hysterectomy : a Double Blind Controlled Study

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ABSTRACT

Background: Various adjuvants are being used with local anesthetics for prolongation of intraoperative and postoperative analgesia. Dexmedetomidine, the highly selective alpha 2 adrenergic agonist is a new neuraxial adjuvant gaining popularity.
Settings and Design: The study was conducted in prospective, double blind manner. It included 120 American Society of Anesthesiology (ASA) class I and II patients undergoing abdominal hysterectomy under spinal anesthesia after approval from hospital ethics committee with written and informed consent of patients.
Materials and Methods: The patients were randomly allocated into four groups (30 patients each). Group LS received 12.5mg Levobupivacaine with normal saline, group LF received 12.5mg Levobupivacaine with 25mcg fentanyl, group LC received 12.5mg of Levobupivacaine suplemented 30mcg clonidine, and group LD received 12.5mcg Levobupivacaine plus 5mcg dexmedetomidine. The onset time to reach peak sensory and motor level , the regression time of sensory and motor block, hemodynamic changes, and side effects were recorded.
Results: Patients in Group LD had significantly longer sensory and motor block times than patients in Groups LC, LF, and LS with Groups LC and LF having comparable duration of sensory and motor block. The meantime of two segment sensory block regression was 147±21 min in Group LD, 117±22 min in Group LC, 119±23 min in Group LF, and 102±17 in Group LS (P>0.0001). The regression time of motor block to reach modified Bromage zero (0) was 275±25,199±26,196±27,161±20 min in Group LD, LC, LF, and LS, respectively (P>0.0001).The onset times to reach T6 dermatome and modified Bromage 3 motor block were not significantly different between the groups. Dexmedetomidine group showed significantly less and delayed requirement of rescue analgesic.
Conclusions: Intrathecal dexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand of rescue analgesics in 24 h as compared to clonidine, fentanyl,or lone Levobupivacaine.

KEYWORDS α2-adreno receptor agonist, Levobupivacaine, clonidine, dexmedetomidine, fentanyl, spinal-anesthesia.

Introduction: Sub-arachnoid blockade is the most commonly used regional anesthetic technique for Hysterectomy. Various adjuvants are being used with local anesthetics for prolongation of intraoperative and postoperative analgesia. However, there use is thwarted either due to the adverse effects of adjuvants or unreliable postoperative analgesia. Most of the clinical studies about the intrathecal α-adrenergic agonist are related to clonidine [1] Dexmedetomidine, a highly selective α adrenergic agonist has evolved as a panacea for various applications and procedures in the perioperative and critical care setting[2] It is also emerging as a valuable adjunct to regional anesthesia and analgesia, where gradually evolving studies can build the evidence for its safe use in central neuraxial blocks[3] . Based on earlier human studies, it is hypothesized that intrathecal 5µg dexmedetomidine would produce more postoperative analgesic effect with Levobupivacaine in spinal anesthesia with minimal side effects[4,5,6,7] In view of few evidences [4,5,6,7] of dexmedetomidine's efficacy as an adjuvant to Levobupivacaine in spinal anesthesia, we strived to explore its usefulness and also compare this new α-adrenergic agonist with the previously established and widely used adjuncts clonidine and fentanyl on the spinal block characteristics in patient scheduled for abdominal hysterectomy.

Materials and Methods: After obtaining approval from the Hospital Ethics Committee along with written and informed consent,120 adults of either sex belonging to American Society of Anesthesiology (ASA) class I and II and scheduled for abdominal hysterectomy under subarachnoid block, were enrolled in this prospective, randomize, and double blinded study. Patients with contraindication to regional anesthesia, history of significant coexisting diseases like ischemic heart disease, hypertension, impaired renal functions, rheumatoid arthritis, and severe liver disease where excluded from this tudy. Presence of pregnant patients, chronic alcoholics and malnourished patients, atrio-ventricular block, incomplete or partial heart-blocks, intake of blockers also precluded us from considering these patients for this study. All patients were examined and investigated a day prior to surgery, and were familiarized with visual analogue scale (VAS)[8] and its use for measuring the post-operative pain. They were advised fasting for 6h and received alprazolam 0.5mg as premedication a night before and 0.25mg in morning on the day of the surgery.

Intraoperative In the operation theatre electrocardiogram (ECG), pulse-oximetry, and non-invasive blood pressure were attached and baseline parameters were recorded and monitoring was initiated. Intravenous(IV) access was secured and all patients were preloaded with ringer lactate 10ml/kg. These patients were randomly assigned using sealed envelope technique to either of the four groups in a double blind manner. The various treatment groups were as per Table1. The study solutions were prepared in a 5ml syringe by anaesthesiologist who then handed them over in a coded form to the attending anesthesiologist blinded to the nature of drug given to him/her. Subarachnoid block was administered at the L3 or L4 vertebral level using 26 gauge Quincke spinal needle with patients in the sitting position under all aseptic precautions. Patients were made supine following the block. The anesthesiologist performing the block recorded the intraoperative data. The onset and duration of sensory block, highest level of sensory block, time to reach the highest dermatomal level of sensory-block, motor block onset, time to complete motor block

recovery, and duration of spinal anesthesia were recorded. The onset of sensory block was defined as the time between injection of intrathecal anesthetic and the absence of pain at the T6 dermatome assessed by sterile pinprick every 2 min till T6 dermatome was achieved. The highest level of sensory block was evaluated by pin prick at mid-clavicular line anteriorly every 5 min for 20 min after the injection, thereafter every 15 min. The duration of sensory block was defined as the time of regression of two segments in the maximum block-height, evaluated by pinprick. The motor level was assessed according to modified Bromage-score:[9] Bromage 0, the patient is able to move the hip, knee, and ankle; Bromage 1, the patient is unable to move the hip, but is able to move the knee and ankle; Bromage2,the patient is unable to move hip and knee, but is able to move the ankle; and Bromage 3, the patient is unable to move the hip, knee, and ankle. Time for motor block onset was defined as modified Bromage score of 3. Complete motor block recovery was assumed when modified Bromage score was 0. The duration of spinal anesthesia was defined as the period from spinal injection to the first occasion when the patient complained of pain in the postoperative period. All durations were calculated considering the time of spinal injection as time zero. Surgery was allowed to commence on achieving adequate sensory block height (T6). Vitals were recorded 5min before intra-thecal injection; 5, 10, 15, 20,and 25 minutes after and subsequently every 15 minutes. Pain scores using VAS were recorded 5min before intra-thecal injection, after the start of surgery, and subsequently every 15 min till the surgery was over; and thereafter VAS was assessed in the post operative period. IV fluids were given to maintain the blood pressure. Hypotension was defined as a decrease in systolic blood pressure (SBP) by 30% from base line and was treated with IV boluses of 6mg ephedrine or crystalloid fluids. Heart-rate (HR) less than 50 beats/min was corrected using 0.6mg of IV atropine sulfate. The incidence of pruritus, nausea, vomiting, and sedation were recorded. De Kock sedation scale [10] was used: 1=patient somnolent but responding to verbal commands; 2=patients somnolent, not responding to verbal commands but responding to manual stimulation; and 3=patient somnolent, not responding to verbal commands or manual stimulation.

Postoperative Motor block recovery (modified Bromage score of zero), sensory block regression were assessed every 15 min after completion of surgery till the time of regression of two segments in maximum block in the post anesthetic care unit (PACU) alongwith the vital signs and VAS scores. Any patient showing VAS more than or equal to 3 was administered a supplemental dose of IV Tramadol 50mg. The amount required by the patients in the next 24 h was recorded in all the groups.

Statistical analysis Data obtained were tabulated and analyzed using Statistical Package for Social Science (SPSS15.0 evaluation version). To calculate the sample size, a power analysis of = 0.05 and = 1.00 showed that 30 patients were needed per study group to detect an increase of 30 min difference between the median duration of spinal sensory block between the groups. Data was expressed as means and standard deviation (SD), medians and ranges, or numbers and percentages. For categorical covariates (ASA class nausea/vomiting ,use of additive analgesia, hypotension, and bradycardia) Chi-square test or Fisher's exact test was used as appropriate, with P value reported at the 95% confidence interval(CI) . Continuous covariates (age, duration of surgery) were compared using analysis of variance (ANOVA) . If P value was significant, then Tukey's honest significant difference (HSD) post-hoc multi comparison test was applied to see the significance between each pair of groups.

Results: All patients (n=120) completed the study; there was no statistical difference in patients demographics or duration of surgery as shown in Table 2. When compared the time of onset of both, sensory and motor-block was statistically insignificant in all the four groups (P<0.05) . T6 was the highest level of sensory block attained at 10.1±3.5, 9.6±2.9, 9.5±3.0,10.3±3.3min after injection in 26.6, 3.3, 23.3, and 26.7% patients in group LS, LF, LC, and LD respectively. However 63.3, 80.0, 73.3, and 70.0% of patients in groups LS , LF, LC, and LD had sensory block to a level of T8 at 7.8±1.8, 8.6±1.5, 8.3±2.8, 8.3±2.4min after the injection (statistically insignificant). T6 sensory level was achieved in all patients. However, there were patients with level progressing further to the highest sensory level of T4. The duration of sensory and motor block was significantly prolonged in group LD as compared to other groups (P>0.0001). Group LS had a statistically significant shorter duration of both sensory and motor block when compared with LF, LC, and LD (P>0.0001). However, group LC and LF were comparable with no statistical differences between these two groups [Table 3]. The duration of spinal anesthesia was shorter in group LS as compared to the other groups with significantly delayed requirement in the group LD (P>0.0001) [Table 3]. The mean values of mean arterial pressure (MAP) and heart rate (HR) were comparable between the four groups through-out the intra-operative and postoperative periods. None of the patients experienced respiratory distress at any point of time. All patients had peripheral oxygen-saturation (SpO_2) greater than 96 % at all the times and did not require additional oxygen in PACU. No significant difference was observed in the sedation scores with patients in all groups having score of 1. Pruritus was observed only in group LF in four patients (13.3%) at different intervals of time, but it did not reach statistical significance (P=0.10). In group LS, one patient had nausea score=4 at 5 min and two patients in group LC had nausea score=4 at 15 and 55 min and required treatment intraoperatively (P=0.36). However, one patient in group LF had postoperative vomiting requiring treatment with ondansetron. Two of the patients in the group LC and one patient in group LD had bradycardia and required treatment with atropine (P>0.05). There was no incidence significant hypotension or respiratory depression in patients in any of the groups. Lower VAS values (>3) were observed in all the groups during the whole duration of the surgery and none of the patients required additional analgesics intra-operatively. Postoperative VAS scores and total analgesic requirement in 24 h were minimal in group LD (P value: LD vs LF 0.009, LD vs. LC 0.05). Group LS had a statistically significant requirement of rescue analgesic as compared to group LF, LC, and LD with the P value of 0.04, 0.008, and 0.005, respectively. Group LF and LC were comparable in total analgesic requirement over 24h.

Table 1

Group LS	Intrathecal (I/T) .5% isobaric levo-bupivacaine 12.5 mg(2.5 ml) + preservative free normal saline (0.5ml)
Group LF	Intrathecal (I/T) .5% isobaric levo-bupivacaine 12.5 mg(2.5 ml) + fentanyl 25mcg (0.5ml)
Group LC	Intrathecal (I/T) .5% isobaric levo-bupivacaine 12.5 mg(2.5 ml) + clonidine 30mcg (0.2ml) + preservative free normal saline (0.3ml)
Group LD	Intrathecal (I/T) .5% isobaric levo-bupivacaine 12.5 mg(2.5 ml) + dexmedetomidine5mcg (0.05ml) + preservative free normal saline (0.45ml)

Table 2

Variable	Group LS (n=30)	Group LF (n=30)	Group LC (n=30)	Group LD (n=30)	P Value
Age (years)	33.5+-14.8	38.1+-13.5	37.0+-12.0	37.8+-15.6	0.50
ASA (I-II)	28:2	28:2	26:4	26:4	0.19
Height (cm)	169.3+-2.3	168.2+-6.0	170.6+-5.6	169.6+-5.5	0.47
Weight (kg)	63.6+-11.2	67.2+-8.7	69.3+-10.7	66.6+-7.9	0.16
Duration of Surgery (min)	93.8+-32.4	101.6+-36.3	99.8+-34.5	110.8+-33.7	0.29

Table 3

Variable (min)	Group LS (n=30)	Group LF (n=30)	Group LC (n=30)	Group LD (n=30)	P value
Time of Onset of Sensory block	7.8+-1.8	8.6+-1.5	8.3+-2.8	8.3+-2.4	0.112
Time of Onset of motor block	9.2+-2.9	9.0+-3.0	9.8+-3.6	9.7+-3.2	0.086
Time To reach maximum sensory level	10.1+-3.5	9.6+-2.2	9.5+-3.0	10.3+-3.3	2.22
Duration of Sensory Block	102.3+-17.2	119.5+-22.7	117.0+-21.8	146.7+-20.5	0.0001
Duration of Motor Block	161.5+-19.8	196.0+-26.8	198.7+-26.4	273.3+-24.6	0.0001
Duration of Spinal Anaesthesia	183.0+-31.0	235.5+-38.3	242.3+-54.2	295.5+-44.3	0.0001