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ORIGINAL ARTICLE

A Comparative Study of Intrathecal Fentanyl and Dexmedetomidine as Adjuvants to Hyperbaric Levobupivacaine 0.5% and Hyperbaric Levobupivacaine 0.5% Alone in Infraumbilical Surgeries

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ABSTRACT

Introduction: Spinal anesthesia is the most common approach used for lower abdominal surgeries. Levobupivacaine 0.5% and racemic bupivacaine 0.5% are equally effective in spinal anesthesia. Dexmedetomidine (a highly selective alpha-2 adrenergic agonist) and fentanyl (short-acting synthetic opioid) are effective intrathecal adjuvants. The aim of our study was to evaluate onset and duration of sensory and motor block, duration of postoperative analgesia, and side effects on addition of dexmedetomidine and fentanyl as adjuvants to hyperbaric 0.5% levobupivacaine along with the control group.

Materials and methods: Ninety patients of American Society of Anesthesiologists (ASA) grade I/II undergoing infraumbilical surgery were studied in a prospective, double blind, controlled study. Levobupivacaine was made hyperbaric by adding 1 mL of 25% dextrose to 12.5 mg levobupivacaine. Patients were randomly allocated to receive either 12.5 mg hyperbaric levobupivacaine + normal saline (group A, n = 30) or 12.5 mg hyperbaric levobupivacaine + 25 µg fentanyl (group B, n = 30) or 12.5 mg hyperbaric levobupivacaine + 5 µg dexmedetomidine (group C, n = 30) intrathecally.

Results: Patients in the dexmedetomidine group had significantly longer sensory and motor block time than patients in the fentanyl and control groups. Mean time of sensory regression to S1 was 161.2 ± 14.6, 180.3 ± 6.2, and 472.5 ± 8.7 minutes in groups A to C respectively ($p < 0.0001$). Duration of analgesia was prolonged to 259.4 ± 12.8 minutes in group C as compared with 114.0 ± 14.3 and 161.8 ± 8.5 minutes in the control and fentanyl group respectively ($p < 0.0001$).

Conclusion: Intrathecal 5 µg dexmedetomidine seems to be an attractive alternative to 25 µg fentanyl as adjuvant to 0.5% hyperbaric levobupivacaine in spinal anesthesia. It is associated with prolonged motor and sensory block and provides good quality of intraoperative analgesia and extended duration of postoperative analgesia as compared with fentanyl.

Keywords: Dexmedetomidine, Fentanyl, Levobupivacaine, Spinal anesthesia.

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INTRODUCTION

Pain is a dehumanizing experience that destroys the soul. Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[1] Relief of pain during surgery is the main aim of anesthesia. Any expertise acquired in this field should be extended into the postoperative period. Severe postoperative pain is a well-known morbidity and is the most distressing complication of surgery. Many options are available for the treatment of postoperative pain, including systemic (i.e., opioid and nonopioid) analgesics and regional techniques.

Spinal anesthesia is a commonly used technique for lower abdominal surgeries. Nowadays, apart from lignocaine and bupivacaine, levobupivacaine and ropivacaine are commonly being used for neuraxial anesthesia. Levobupivacaine is the S-enantiomer of bupivacaine with similar onset of sensory and motor block. Duration of analgesia is prolonged with rapid recovery from motor block. It is better in safety profile, i.e., it has less central nervous system and cardiac toxicity, and there are lesser episodes of hypotension.[2]

However, spinal anesthesia using only local anesthetics is associated with relatively short duration of action, and thus, early analgesic intervention is needed in the postoperative period. A number of adjuvants, such as midazolam, clonidine, and fentanyl, have been used to prolong the duration of spinal anesthesia. Fentanyl is a potent, short-acting, highly lipophilic, synthetic opioid analgesic. It has been commonly used as an adjuvant for postoperative analgesia.[3] Dexmedetomidine, a selective α2-agonist, provides stable hemodynamic conditions and good quality of intraoperative and prolonged postoperative analgesia with minimal side effects.[4]

Until now, there has been no study done evaluating the effect of adding fentanyl or dexmedetomidine to hyperbaric levobupivacaine and comparing with control group. Our study was designed to assess and compare the effect of intrathecal fentanyl and dexmedetomidine as adjuvants to hyperbaric levobupivacaine 0.5% and hyperbaric levobupivacaine 0.5% alone in patients undergoing infraumbilical surgeries.

MATERIALS AND METHODS

The study was conducted with due permission from the institutional ethical committee. Informed written consent from all the patients was obtained before participation. Expecting the minimum detectable difference in total analgesia time to be 82 minutes with residual standard deviation (SD) 101 minutes (as per seed article – Gupta et al[5]), the sample size was calculated as 30 subjects for each group at alpha error 0.05 and power 80%.

Ninety patients of either sex, aged between 30 and 50 years, with American Society of Anesthesiologists (ASA) grade I/II presenting for infraumbilical surgery, such as appendicectomy, herniorraphy, abdominal hysterectomy (duration 60–90 minutes), were included in the study. The patients were randomized into one of the three groups (n = 30/group) using chit in box method.

The patients were preloaded with lactated Ringer's solution 10 mL/kg. They were monitored with pulse oximetry, automated noninvasive blood pressure, and electrocardiogram. Hyperbaric solution of levobupivacaine was prepared by mixing 2.5 mL of 0.5% preservative-free isobaric levobupivacaine and 1 mL of 25% dextrose. This gave 3.5 mL of hyperbaric solution of levobupivacaine. Total volume of 4 mL of anesthetic solution was injected in all patients.

Spinal anesthesia was given at L3–L4 interspace with the patient in left lateral position using a 25-Gauge Quincke needle under strict aseptic conditions. Anesthetic drug was given according to the allocated group to which the patient belonged.

- Group A (levobupivacaine control group): Patients received 12.5 mg (2.5 mL) of 0.5% levobupivacaine + 1 mL of 25% dextrose + 0.5 mL of normal saline intrathecally.
- Group B (fentanyl group): Patients received 12.5 mg (2.5 mL) of 0.5% levobupivacaine + 1 mL of 25% dextrose + 25 µg (0.5 mL) fentanyl intrathecally.
- Group C (dexmedetomidine group): Patients received 12.5 mg (2.5 mL) of 0.5% levobupivacaine + 1 mL of 25% dextrose + 5 µg dexmedetomidine diluted in 0.5 mL of normal saline intrathecally.

Patients were immediately placed in a supine position following the injection with a 15° head down tilt to achieve level of block of T5–T6. Oxygen was administered by mask at 4.0 L/minute. Vitals were checked every 2 minutes for first 10 minutes, then every 10 minutes till surgery, and then every 30 minutes for 4 hours postoperatively. The level of sensory block was tested by pinprick bilaterally at mid-clavicular line which was done every minute till the maximum sensory level was achieved and then after 1 hour at half an hour interval. Onset of sensory block was taken as the time taken to attain sensory level of T6 dermatome. Time of onset of motor block was assessed using Bromage scale. Onset of motor block was taken as the time taken to achieve Bromage grade 3 block from the time of subarachnoid injection. The incidence of side effects, such as nausea, vomiting, pruritis, respiratory depression, was also noted.

Postoperatively, patients were monitored to assess time to two-segment regression, sensory regression to S1, and duration of motor blockade. Visual analog scale (VAS) score (Table 1) was serially assessed at half an hour interval starting from 60 minutes till the patient complained of pain (VAS > 3) (Table 1).

Duration of effective analgesia was measured as the time from intrathecal drug administration to the patient's VAS score > 3 and was recorded in minutes. Patient's VAS > 3 and administration of rescue analgesia constituted the end point of the study.

Statistical analysis was performed with Statistical Package for the Social Sciences, Version 19.0 for Windows statistical software package (SPSS Inc., Chicago, USA). Categorical data, i.e., type of surgery and the incidence of adverse events, are presented as numbers and compared by chi-square test. Groups are compared for demographic data (age, weight), duration of surgery, time for two-segment regression, VAS score, total duration of sensory and motor block, and duration of analgesia by analysis of variance and paired t-test. Probability was considered to be significant if less than 0.05. Data are represented as mean and SD.

RESULTS

The groups were comparable with respect to age, weight, height, and ASA physical status ($p > 0.05$). There was no significant difference with respect to type and duration of surgery among the groups (Table 2).

Table 1: Visual analog scale score

Score	*Criteria*
0	No pain
1–3	Mild pain
4–6	Moderate pain
7–9	Severe pain
10	Worst imaginable pain

Table 2: Demography

Variable	*Group A*	*Group B*	*Group C*	*p-value*	*Significance*
Age (years)	39.7 (6.7)	38.3 (6.2)	38.6 (6.5)	>0.40	NS
Weight (kg)	57.0 (3.6)	56.7 (3.8)	57.0 (4.0)	>0.72	NS
Height (cm)	158.0 (3.6)	159.2 (4.3)	158.7 (3.8)	>0.25	NS
ASA Grade I:II	27:3	27:3	26:4	>0.69	NS
Duration of surgery	75.3 (7.7)	72.9 (8.3)	71.7 (8.6)	>0.09	NS
Type of surgery					
TAH	18	17	17	>0.86	NS
Inguinal hernia	6	5	7	>0.56	NS
Urinary bladder and ureteric surgery	2	4	3	>0.41	NS
Appendicectomy	4	4	3	>0.70	NS

Values given as mean (SD); TAH: Total abdominal hysterectomy; NS: not significant

Table 3: Characteristics of sensory and motor block

Variable	*Group A*	*Group B*	*Group C*	*p-value*	*Significance*
Onset of sensory block (minutes)	7.8 (1.5)	7.3 (1.4)	7.1 (1.4)	>0.06	NS
Onset of motor block (minutes)	8.9 (1.1)	8.5 (1.1)	8.3 (1.3)	>0.09	NS
Time to two-segment sensory regression (minutes)	81.3 (7.2)	85.5 (7.0)	118.5 (9.1)	<0.02	S
Duration of analgesia (minutes)	114.0 (14.3)	161.8 (8.5)	259.4 (12.8)	<0.0001	HS
Time for sensory regression to S1 (minutes)	161.2 (14.6)	180.3 (6.2)	472.5 (8.7)	<0.0001	HS
Duration of motor block (minutes)	142.2 (5.5)	144.0 (5.9)	421.6 (10.6)	A *vs* B=0.22	NS
				A *vs* C<0.0001	HS

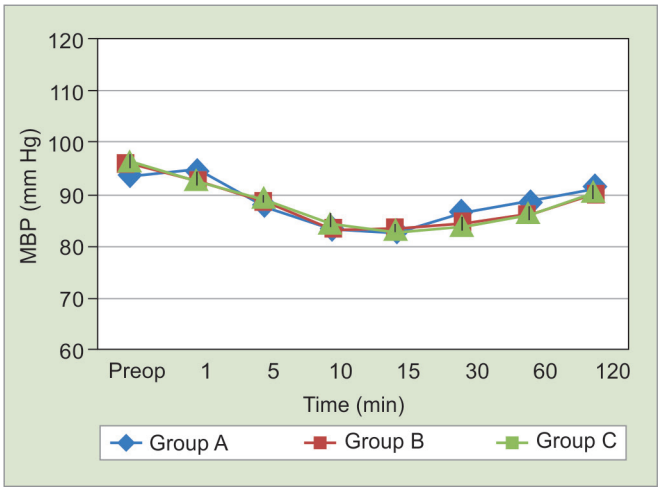
Values given as mean (SD); NS: not significant; S: significant; HS: highly significant

Table 3 summarizes the sensory and motor block characteristics in the three groups. The time for onset of sensory block and motor block was similar in the three groups ($p > 0.05$). Block regression was significantly slower in group C as compared with the other two groups. Hence, time for two-segment regression and sensory regression to S1 was significantly prolonged in dexmedetomidine group as compared with fentanyl and control groups ($p < 0.0001$). Duration of analgesia was also significantly longer in dexmedetomidine group as compared with groups A and B ($p < 0.0001$). Addition of fentanyl did not show prolongation of motor block ($p = 0.22$), whereas dexmedetomidine caused significant prolongation of duration of motor block as compared with the control group ($p < 0.0001$).

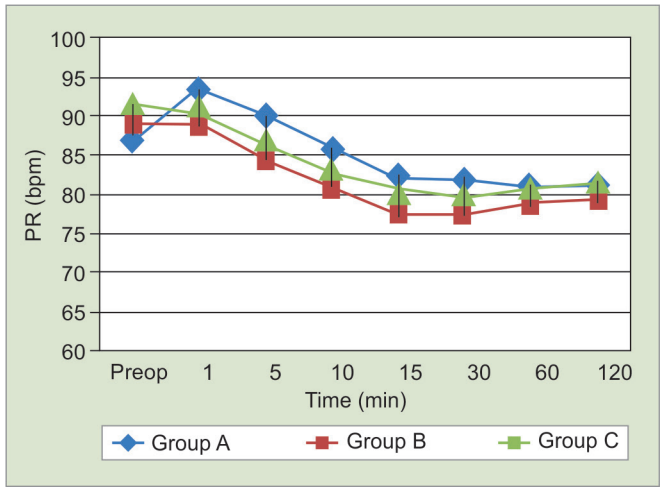
Patients in all the three groups remained hemodynamically stable and the trends of blood pressure and pulse rate were comparable in the three groups ($p > 0.05$) (Graphs 1 and 2). The incidence of side effects was also similar in the three groups (Table 4).

DISCUSSION

It is well recognized that postoperative pain is most often being undertreated. The routine use of regional anesthesia for lower abdominal surgeries is associated with



Graph 1: Trends of mean blood pressure in the three groups



Graph 2: Trends of pulse rate in the three groups

Table 4: Side effects

Side effects	*Group A*	*Group B*	*Group C*	*p-value*
Hypotension	3	3	4	>0.70
Bradycardia	2	2	3	>0.65
Nausea, vomiting	2	1	1	>0.56
Respiratory depression	0	0	0	–
Pruritis	0	0	0	–

a short duration of analgesia postoperatively. Although many drugs (morphine, nalbuphine, clonidine vasoconstrictors like epinephrine and phenylephrine) have been used as an adjuvant to local anesthetics, the high incidence of side effects (respiratory depression, sedation, cardiovascular instability, nausea–vomiting, pruritis, and urinary retention) and relative ineffectiveness resulted in reluctance to administer these drugs.

Fentanyl is a short-acting, lipophilic, μ-receptor agonist opioid. It has been used intrathecally as an adjuvant for over two decades.[6,7] In the spinal cord, μ-receptors are located with highest concentration in the substantia gelatinosa, and direct application of fentanyl to these receptors creates intense analgesia by inhibiting presynaptic release of substance P in primary sensory neurons. This is mediated by a decrease in intracellular cyclic adenosine monophosphate levels, associated with a G-protein-mediated increase in K^+ influx and inhibition of Ca^{2+} influx, leading to reduced neurotransmitter release, hyperpolarization of neuronal membranes, and decreased synaptic transmission.[8] Singh et al[9] observed that the addition of 25 μg fentanyl to hyperbaric bupivacaine intrathecally results in significant prolongation of time for two-segment sensory regression and sensory regression to L1 dermatome. In our study, we also observed similar results with 25 μg fentanyl and 12.5 mg hyperbaric levobupivacaine. Duration of analgesia and sensory regression to S1 were significantly prolonged without any effect on duration of motor block. Lee et al[10] studied the dose sparing effect of fentanyl as an adjuvant and concluded that 2.3 mL of 0.5% levobupivacaine with fentanyl 15 μg is as effective as 2.6 mL of 0.5% levobupivacaine alone in spinal anesthesia for urological surgery.

For α2-adrenergic drugs, the mechanism of analgesia is not clearly known. Clonidine has been commonly used as an adjuvant for postoperative analgesia.[11] Dexmedetomidine is a new highly selective α2-agonist having eight times greater specificity for α2-receptor than clonidine, with an α2/α1 binding affinity ratio of 1620:1. In our study, the intrathecal 5 μg dose of dexmedetomidine was selected on the basis of previous human studies.[5,12]

Esmaoğlu et al[13] concluded in their study that intrathecal 3 μg dexmedetomidine in addition to levobupivacaine for spinal anesthesia shortens sensory and motor block onset time and prolongs block duration without any significant adverse effects. However, in our study, we did not find any significant difference in the onset time of sensory and motor block. The prolongation of two-segment sensory regression, sensory regression to S1, and duration of motor block was statistically highly significant. Also, the duration of analgesia was prolonged to 259.4 ± 12.8 minutes as compared with 114.0 ± 14.3 and 161.8 ± 8.5 minutes in control and fentanyl groups respectively. Similar results were observed by Gupta et al[5] and Al-Mustafa et al.[4]

In our study, hypotension and bradycardia were more in the dexmedetomidine group as compared with the other two groups, but it was not statistically significant. No patient experienced pruritis and respiratory depression in any group. Dexmedetomidine also has antishivering properties as observed by Maroof et al.[14] We too did not find any incidence of shivering in the three groups.

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