Original Research Article

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Comparison of Fentanyl with Preservative Free Midazolam as an Adjuvant to Levobupivacaine in Patients Undergoing Total Abdominal Hysterectomy under Spinal Anaesthesia

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Abstract

Background: This prospective randomized double-blind study was designed to compare the analgesic efficacy and safety of intrathecal midazolam versus fentanyl as an adjunct to levobupivacaine for total abdominal hysterectomy. *Methods:* Sixty ASA grade I–II female patients undergoing total abdominal hysterectomy were randomly allocated into two groups. Group 1 (LM)– 3 ml of 0.5% isobaric levobupivacaine+2mg(0.4ml) of preservative free midazolam was given and in Group 2 (LF)- 3ml of 0.5% isobaric levobupivbacaine+12.5ug fentanyl(.25ml)+0.15ml of normal saline was given. The onset and duration of sensory and motor blockade, postoperative pain and the time to 1st rescue analgesia was noted. Patients were observed for hypotension, bradycardia, sedation, respiratory depression, pruritus, nausea and shivering. *Results:* The onset of sensory blockade was early in LM group(p- value <0.01). while duration of sensory blockade was comparable between the two groups(p-value >0.05). Onset of motor blockade was again early in LM group as compared to LF group (p value=0.007). The duration of rescue analgesia was significantly prolonged in group LM as compared with group LF (p-value <0.001). The incidence of pruritis was more in group LF while respiratory depression was more in LM group. *Conclusions:* Addition of midazolam to intrathecal levobupivacaine provides early sensory and motor blockade and also prolonged time for rescue analgesia when compared to LF group. The incidence of pruritis was less in LM group while sedation and respiratory depression was more as compared to LF group.

Keywords: Adjuvants-Fentanyl; Midazolam; Anesthesia-Spinal; Total Abdominal Hysterectomy; Rescue Analgesia.

Introduction

Through progress in anaesthetic compounds and equipments spinal anaesthesia has grown in popularity and today has firmly cemented role in modern anaesthesia carrying an acceptably low incidence of major complications [1]. Neuraxial anesthesia provides a better postoperative quality of recovery and analgesia than does general anesthesia in patients undergoing abdominal hysterectomy [2,3].

Levobupivacaine is pure S-enantiomer of racemic bupivacaine and is a new long acting local anaesthetic that has recently been introduced in clinical routine. Its significantly decreased cardiovascular and central nervous system toxicity make it an attractive alternative to bupivacaine [4,5]. Fentanyl prolongs the sensory block without delaying time to void [38]. The literary evidence has established that addition of opioids provides a dose sparing effect of levobupivacaine, with improved quality of the block and less hemodynamic variations [6]. Several investigations have shown that antinociceptive action of intrathecal midazolam is mediated via benzodiazepine GABA-A receptor complex which are abundantly present in lamina II of dorsal horn ganglia of spinal cord. Different doses of midazolam upto 2mg have been found free of any neurotoxicity [7].

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None of the studies to date compared the efficacy of intrathecal midazolam with fentanyl in as an adjuvant to levobupivacaine thereforethe present study was done to compare the efficacy of fentanyl with preservative free midazolam as an adjuvant to intrathecal levobupivacaine in total abdominal hysterectomy.

Material and Methods

After approval from the 'Institutional Ethics Review Committee' and written informed consent, American Society of Anaesthesiology (ASA) grade I-II patients with age group 18 to 65 years (weight 40-70 kg) undergoing total abdominal hysterectomy were included in the study. Patients were randomly divided into two groups of 30 patients each using random allocation software. In Group 1 (LM) -3 ml of 0.5% isobaric levobupivacaine+2mg (0.4ml) of preservative free midazolam was given and in Group 2 (LF)- 3ml of 0.5% isobaric levobupivbacaine +12.5ug fentanyl (.25ml)+0.15ml of normal saline was given.

Patients with history of allergy to drugs used in study, having any contraindication to spinal anaesthesia and pregnant and lactating females were excluded. The patients received 0.5 mg Alprazolam orally at night before surgery. On arrival in the operation theatre standard monitoring of five-lead electrocardiography, non-invasive blood pressure and pulse oximetry was instituted. Intravenous line was secured with 18 G cannula and RL infusion was started Spinal anesthesia was performed at L_{3-4} intervertebral space with a 26-G Quincke needle with patients in sitting position. Once free flow of cerebrospinal fluid was obtained, the study drug was injected slowly over 1-2 minutes. Intraoperative parameters i.e SBP, DBP, MAP and heart rate was monitored and recorded every 3 minutes for 30 minutes and then at every 10 minutes interval till the end of surgery.

The onset of sensory block was assessed from the time of injecting the drug into subarachnoid space till complete analgesia at the level of T_{10}. Level of sensory block was checked by loss of pin prick sensation bilaterally in midclavicular line using 23-gauge hypodermic blunt needle and dermatomal level was tested every 2 minutes until sensory block remained constant for 3 consecutive times. Maximum level achieved was noted. After that sensory level assessement was continued every 10 minutes after one hour of injecting drug till there is two segment regression of the block which was taken as duration of sensory blockade.

The onset of motor block was taken from the time of injecting drug to score of 3 on modified bromage scale. It was assessed every 2 minutes, till complete motor block was achieved as per Modified Bromage Scale,1=total motor block, 2=patient can only move his/her feet, 3= partial motor block, 4= patient can move his/her knees, 5= patient can lift his/her leg but cannot hold the position, 6=no motor block.

Sedation score was given as per Ramsay Sedation Scale every 30 minutes.

Hypotension recording less than 30% of baseline MBP or SBP <90mm of Hg was treated with the help of intravenous fluid bolus and incremental doses of mephentermine 6mg i.v. If bradycardia (heart rate less than 50 beats per minute) occurs, it was treated with i.v. injection of atropine 0.6mg. Respiratory depression (if RR< 8 breath/min or SpO_2<90%) was treated with oxygen supplementation.

Duration of analgesia was assessed by Visual Analogue Scale. Injection Tramadol 50mg i.m was given as rescue analgesia when patients VAS score reached more than or equal to 4 and the time was recorded.

One patient in each group due to uneven sensory block was given general anaesthesia. So in each group 29 patients were studied. The data of the study were recorded in the record chart and results were evaluated using statistical tests. The descriptive were presented in the form of mean and S.D along with other dispersion measures whereas inferential analysis was summarized through student t-test (independent t-test) and chi-square test for count and nominal variables respectively.

Results

Demographic data for age and weight between the two groups was comparable. There was no statistically significant difference between the two groups in respect to baseline parameters i.e. HR, SBP, DBP, MBP, SpO_2 (Table 1).

The onset of sensory block was delayed in the group LF and this difference was found to be highly significant statistically (p- value <0.01). Time to achieve maximum sensory level was again delayed in Group LF which was significant statistically (p<0.05). Time for two segment regression from the highest sensory level was comparable in LF and LM group respectively (Table 2).

The time for onset and duration of motor block was again delayed in Group LF as compared to LM group (p value <0.05) (Table 2).

The sedation scores were found to be higher for group LM than LF at 30 and 60 minutes.

Respiratory depression was in 17.2% patients in LM group as compared to LF group in which no patient had respiratory depression (p value=0.05). Pruritis was seen in 20.7% patients of LF group as compared to none in LM group (p value= 0.031). Rest no significant difference was found between two groups in respect of nausea, bradycardia, shivering, hypotension (Table 3, Figure 2).

No statistically significant difference in VAS score was found between the two groups. Time for rescue analgesia LM group was recorded as 263±13.58 minutes whereas for LF group was 200±14.40 minutes, which was found to be highly statistically significant (p-value <0.001) (Table 2, Figure 1).

Table 1: Demographic parameters of two groups

Parameter	LM	LF	P value
Age	44.52± 6.78	44.62± 6.01	0.381
Weight	56.62±3.30	56.24±5.03	0.735

Table 2: Comparison of side effects between the two groups

Parameters	LM (minutes)	LF (minutes)	P value
Time of sensory onset	3.97± 0.98	4.72± 0.88	0.003
Time for max. sensory block	10.52± 1.18	11.28± 1.28	0.023
Time for 2 segment regression	133.62± 6.40	136.21± 6.75	0.14
Time of motor onset	6± 1.41	7.03± 1.38	0.007
Time for max. motor block	8.14± 1.77	9.03± 1.38	0.035
Time for rescue analgesia	263.28± 13.58	200.86± 14.40	0.001

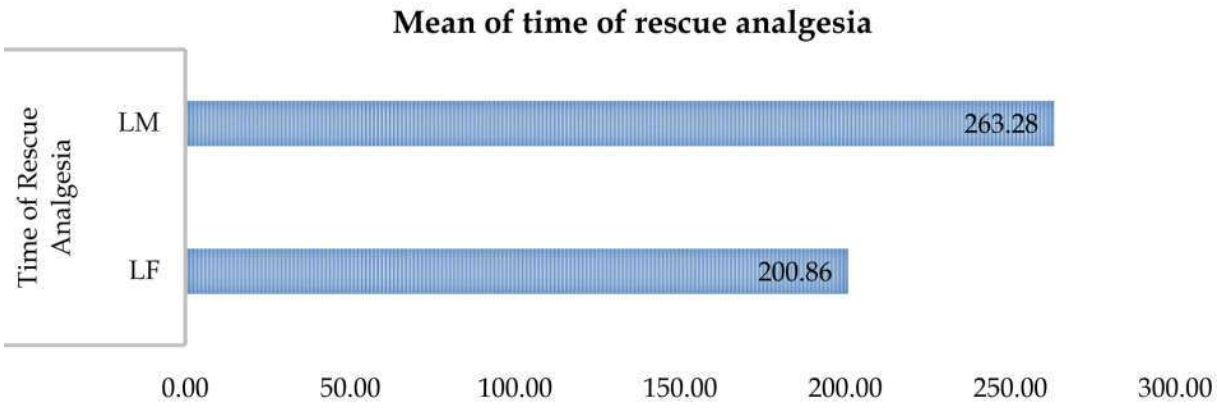

Fig. 1:

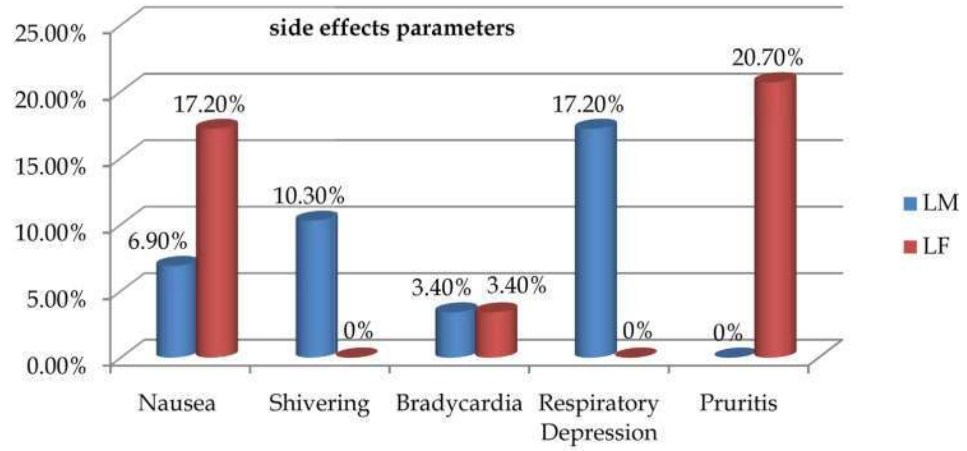

Fig. 2:

Discussion

In the present study efficacy of intrathecal midazolam 1mg and intrathecal fentanyl 12.5 ug as an adjuvant to levobupivacaine were compared. Previously there has been no such comparison.

In our study mean onset time of sensory block (in minutes) was 4.72±0.88 minutes in group LF, and 3.97± 0.98 minutes in group LM,this difference was found to be highly significant statistically (p- value <0.01). Compared with our study LF group had similar sensory onset time in studies done by Guler et al. [8], Attri et al.[9], Goyal et al. [10]. Compared to our study Bharti et al. [11] also found early onset of sensory block in midazolam group as compared to fentanyl group but was not statistically significant. And also they found duration of sensory block was comparable between the two groups [11]. As compared to LM group in our study Parthasarathy [12] had similar time of regression.

Mean onset time of motor block in group LF was 7.03±1.38 minutes and in group LM was 6.00± 1.41minutes. It was again delayed in LF group. Compared to our study Bharti et al. [11] also found earlier onset of motor blockade in midazolam group as compared to fentanyl. In contrast to our study Kurmunadh et al. [13], Elfawal et al. [14], Asim et al. [15] and Bhure et al. [16] found no difference between midazolam and fentanyl group in regard to duration of onset of motor blockade. This may be due to difference in doses (fentanyl 25 ug).

Ramsay Sedation Score was noted every 30 minutes for assessment of sedation in our study. The scores were found to be higher for group LM than LF group at 30 and 60 minutes (p value < 0.05). Compared to our study Bhure et al found sedation in 20% cases in midazolam group and none in fentanyl group [16]. Similar to our study sedation was more in bupivacaine plus midazolam group as compared to bupivacaine alone in study conducted by Parthasarathy in patients undergoing total abdominal hysterectomy [12].

No significant difference was found between LF and LM group in respect to hypotension and bradycardia. Compared to our study, the studies conducted by Kurmanadh et al., Elfawal et al., Asim et al didn't find any difference in incidence of hypotension and bradycardia between midazolam and fentanyl group [13,14,15].

Compared to our study Kurmanadh et al. [13] and Asim et al. [15] also found longer duration of rescue analgesia by midazolam group as compared to fentanyl group, but was not statistically significant may be because of higher doses of fentanyl used in these studies. Compared to our study study by Brahambhatt et al. [6] showed similar time (220.62±16.25 min) of rescue analgesia in LF group.

In our study 17.2% patients in group LM developed respiratory depression but none of the patients in group LF had respiratory depression (p-value= 0.132). In studies by Guler et al. [8], Goyal et al. [10] and Attri et al. [9] in LF group none had respiratory depression and is comparable to our study. Comparable to our study Parthasarthy in his study also found increased incidence of respiratory depression in midazolam group. But percentage was high i.e. 90% may be due to high dose of midazolam used (1.5 mg) in his study [12].

In our study in LF group 20.7% patients suffered pruritus and none was reported in group LM (p-value= 0.031). Similarly high incidence of pruritis was found in fentanyl group as compared to midazolam group in various studies by Kurmunadh et al., Elfawal et al., Asim et al. [13,14,15].

Conclusion

Hence after this study we conclude that preservative free midazolam when added to isobaric levobupivacaine in spinal anaesthesia is better option than fentanyl in terms of early sensory and motor block and prolonged postoperative pain relief, less incidence of pruritis and similar stable heart rate and blood pressure. Only disadvantage of midazolam as an adjuvant to levobupivacaine is more sedation and respiratory depression when compared to fentanyl as an adjuvant to isobaric levobupivacaine. But larger trials of similar drugs should be undertaken before accepting or refuting this study.

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