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Anesthesiology

KEY WORDS: Intrathecal Fentanyl, Intrathecal Midazolam, gynecological surgeries.

A COMPARISON OF INTRATHECAL FENTANYL BUPIVACAINE AND MIDAZOLAM BUPIVCAINE WITH CONVENTIONAL BUPIVACAINE SPINAL ANESTHESIA ON THE QUALITY OF SUBARACHNOID BLOCK AND PERIOPERATIVE ANALAGESIA IN GYNAECOLOGICAL SURGERIES.

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ABSTRACT

Background: There is increased expectation of postop analgesia from anesthetist, especially after awareness and understanding amongst general population. Pre-emptively, drugs aimed at pain relief can be administered intrathecally, mixed with local anesthetics, the advantage being familiar technique, single shot injection along with the block. **Method:** This randomized double blind prospective study was conducted on 120 adult female patients of ASA 1 or 2, between the age groups of 20-60 years height of 135-170 cm who were to undergo gynecological surgeries. between 2010 to 2014 in the Gynecology OT at the SaiSiddhi Hospital & Modi Hospital Mulund Mumbai, Anesthesia Department. Patients were Randomly assigned to three groups each receiving 3.9ml of total volume in SA. Group F- Intrathecal Heavy bupivacaine0.5% 17.5mg(3.5 ml)+20 mcg Fentanyl(0.4ml) Group M- Intrathecal Heavy bupivacaine0.5% 17.5mg(3.5ml)+ 2mg Midazolam(0.4ml) Group C- Intrathecal heavy bupivacaine 0.5%17.5mg(3.5ml)+0.4ml Normal saline. **Result:** The time taken to achieve both sensory and motor blockade was significantly less in the Fentanyl(F) group as compared to Midazolam(M) and Control(C) group. Pulse rates are lower in F group from 10 mins to 4 hours &after 4-6 hours though statistically significant not clinically. Pulse in the M and C groups are comparable at all times. Blood pressures also are statistically lower in M and F group from 10 mins to up to 3 hours as compared to C group.2 segment recession was also statistically and clinically higher in F and M group. Duration of analgesia (request for rescue analgesia) was higher in all study groups, However the 24hour analgesia consumption was comparable in all the three groups. The route of surgery- abdominal approach required more analgesic doses in all the groups though with the F group required lesser compared to the M & C group. **Conclusion:** Onset of sensory level was faster in Fentanyl group than other two groups. Addition of Intrathecal fentanyl and Midazolam increases the duration of surgical anesthesia. Duration of post op analgesia was not increased by more than 1 to 1.5 hours. There was no difference in post operative analgesia requirement across all the three groups. Intrathecal Fentanyl appears to be more useful in abdominal surgeries, where visceral pain is the predominant component.

INTRODUCTION:

Since its first use, for surgery, in 1898, by August Bier, Spinal Anesthesia has been ever evolving and still is the method of choice of anesthesia for surgeries on lower half of the body.(1,2,3). Because of its rapid action, efficacy, minimal effects on mental status, decreased risk of vomiting, preservation of airway, it is very high with regards to patient safety when chosen correctly. The patient safety, efficacy, along with cost effectiveness makes it choice of anesthesia in developing countries. Heavy Bupivacaine is the most routinely used medicine for Spinal anesthesia.

Various methods of achieving pain relief are employed including preoperative and perioperative, preemptive analgesia. Regional routes are preferred than systemic routes, advantages being site of action(local) and decreaseside effects. (4,5,6)

Many intrathecal additives in form of opioids/nonopioids/ other adjuvants have been tried but none has become established in regular clinical practice.(7,8,6,9)

AIMS and OBJECTIES -

to assess the effect of addition of intrathecal fentanyl to bupivacaine and intrathecal midazolam to bupivacaine as compared to bupivacaine alone on the quality of spinal anesthesia, postoperative analgesia and patient safety and acceptability when used for various gynecological surgeries.

MATERIAL AND METHODS-

After appropriate approval from the Hospital committee, study was done on 120 American society of anesthesiologist (ASA) I-II patients , 20-50 years undergoing elective gynecological surgeries under spinal anesthesia.

Patients refusal to block, presence of bleeding disorders, local infection at the site of block, any history of allergy to study drugs were excluded from the study. Patients in whom spinal anesthesia failed were also excluded from the study. All the patients were explained about the study in preop examination and informed consent was obtained. Pain was assessed on VAS Visual analogue scale 0 to 100((0=no pain; 100 worst imaginable pain). The patients were randomized into three of 40 each using Chit box method.

Group F- Intrathecal Heavy bupivacaine 0.5% 17.5mg(3.5 ml)+20 mcg Fentanyl(0.4ml)

Group M- Intrathecal Heavy bupivacaine 0.5% 17.5mg (3.5ml)+ 2mg Midazolam(0.4ml)preservative free.

Group C- Intrathecal Heavy bupivacaine0.5%17.5mg (3.5ml)+0.4ml Normal saline.

After shifting the patient inside operation theatre, chits were opened by Anesthesiologist not involved in the study to prepare the drug solution according to randomization.

On the day of surgery Patients were Randomized by Chit method and preparation of medicine was done by other Anesthetist, and documented. The Observer and person administering the anesthesia were unaware of the group the patient got assigned to.

Sensory level was checked using sensation to ice /cold. Motor blockade assessed by modified bromage scale. All patients were monitored every 5 mins for BP during surgery, with continuous SPO2 and ECG monitoring.

2 segment recession as documented by light touch and cold sensation was documented.

Duration of analgesia was defined as time of Subarachnoid injection to time of VAS 30.VAS of 30 was cut off for Administration of rescue Analgesia in form of Inj. Tramadol 50 mg.No prophylactic analgesia was given at the end of surgery.

Monitoring continued for vital parameters, sedation score, level of sensory block, motor level and visual analogue score (VAS) were noted every 10 mins for first 2 hours, every 30 mins for next four hours and thereafter 6 hours interval till 12 hours and then after 2 hours.

Analgesia consumption was documented and charted for 24 hours. Duration of sensory block was defined as time from subarachnoid injection to the regression upto L5-S1 assessed by reappearance of sensation at heel and sole of foot.

Duration of motor blockade defined from time of injection to the time patient was able to flex hip, knee and ankle (bromage score 0).

All the observations were charted and later compiled and analysed using ANOVA (Analysis of Variants) and P values <0.05 was considered statistically significant.

OBSERVATIONS

Demographic variables were comparable in all the three groups. The surgeries carried out in all three groups are comparable with respect to abdominal and vaginal approach.

Block Characteristics:

Time taken to achieve both motor and sensory block was significantly less in fentanyl group as compared to midazolam and control group. Complete motor block occurred in all the patients.

Time taken to achieve both motor and sensory block (Table1)

Block Characteristics	Group I (F)	Group II (M)	Group III (C)
Time for maximum sensory block (mean ±SD) in mins	6.76±0.512 *	8.366±0.699	8.29±0.40
Time for Maximum motor blockade (mean±SD) in mins	7.204±0.65	7.98±1.50	8.312±0.44
Motor Block (modified bromage scale)	3	3	3
Maximum sensory block T4-T5 T5-T6 T6-T7 T7-T8	14* 20 6 -	5 26 6 3	3 25 12 -

Higher sensory levels were produced in fentanyl group as compared to control group. 35% of patients in fentanyl group had sensory level of T4,5 as compared to 12.5% in midazolam group and 7.5% in control group.

Pulse rates are lower in the fentanyl group right from 10 mins upto 4 hours. After 4-6 hours though statistically significant the pulse rates were not clinically significantly different. The pulse rates remain comparable in the midazolam and control group except at 2.5 hours where it is only statistically significant.

The blood pressures in both the study groups are lower from 10 mins upto 3-4 hours as compared to control group and later on comparable in all three groups.

Sedation scores were comparable in all groups after 6 hours. prior to that both study groups were more sedated than control groups starting from 10 mins with sedation score of 1 at 10 mins in both the study groups. at 30 mins about 82.5% in F group, 85% in m group and 17.5% in the control groups were comfortably sleeping. None of the patients in any of the groups was excessively sedated.

Time required for 2 segment regression was clinically and statistically significant in both the F and M group compared to C group. Duration of surgery was comparable in all the groups. Sensory block statistically and clinically significant in both study groups longer than control group. Motor blockade had both clinically and statistically longer motor blockade, midazolam had only statistically longer motor blockade not clinically significant.

Time required for 2 segment regression (table-2)

Duration of (in mins)	Group I (F)	Group II (M)	Group III (C)
Surgery	111.87 ± 31.83	97.62 ± 32.89	101.0 ± 20.11
Sensory blockade	215.75 ± 16.72	200.92 ± 16.01	177.87 ± 16.85
Motor blockade	180.37 ± 14.33	157.24 ± 12.56	150.92 ± 13.44

Duration of analgesia (time of intrathecal injection to first rescue analgesia (VAS>/= 30) was both statistically and clinically significant in midazolam and fentanyl group as compared to control group.

Addition of either of the drug appeared to give just extra analgesia of 1to 1.5hours as compared to control group. The mean total analgesic required over 24 hours are comparable in all the three groups.

differential approach to surgery (table-3)

Approach to surgery	No. of analgesics doses	Group I (F)		Group II (M)		Group III (C)	
		No	%	No	%	No	%
Abdominal Approach	3	6	15%*	12	30%	10	25%
	2	14	35%*	6	15%	10	25%
	1	-	-	-	-	-	
Vaginal Approach	3	15	12.5%	1	2.5%		
	2	15	37.5%	18	45%	20	50%
	1			1	2.5%		

The differential approach to surgery- abdominal and vaginal- shows that abdominal route had more analgesic consumption in all three groups (expected), but was less 15% with fentanyl group and 30% in midazolam and 25% in control groups.

Side Effects (table-4)

Side Effects/ complications	Group I (F)	Group II (M)	Group III (C)
Nausea	-	-	5(12%)
Hypotension	2(5%)	-	-
Nausea+ Vomiting	9(22.5%)	2(5%)	-
Shivering	-	4(10%)	6(15%)
GA after 3 hours	-	2(5%)	-
PDPH	1(2.5%)	-	-
Pruritis	-	-	-

2 patients in midazolam group had to be converted to GA after 3 hours of operating time. Nausea and vomiting was higher in F group. 1 patient in 120 had PDPH which was treated conservatively with rest, fluids and analgesics. None of the patients had failed spinal requiring General anesthesia from the very beginning.

DISCUSSION:

Spinal anesthesia is a popular technique of Anesthesia for surgeries on the lower half of the body. Use of various intrathecal adjuncts to spinal anesthesia have been tried with the aim of postoperative analgesia with the added advantage of patient compliance, single time administration and decrease systemic side effects.

Though longer acting drugs like Morphine, hydrophilic opioid, have higher potency and extended duration, it also has major therapeutic liabilities like slow onset, increased incidence of nausea, vomiting, pruritis and risk of delayed respiratory depression, limiting overall utility.

We studied the effects of drugs Fentanyl(opioid) and Midazolam (benzodiazepine), both easily available and short acting when used as adjuncts to bupivacaine intrathecally as compared to bupivacaine alone when used for gynecological surgeries.

Fentanyl, a lipophilic opioid, known to produce rapid onset analgesia has been studied in various doses, when used intrathecally. It has decreased rostral spread, segmental spinal analgesic profile, lack of active metabolites with no risk of delayed respiratory depression, absence of toxicity to nerves, making it attractive drug for intrathecal use.

Belzara et al,(8), investigated fentanyl in dose/kg body weight . average weight was 80 kg , approximated to using 20,40 and 60mcg of the drug intrathecally-with patients receiving 40mcg or more showing increased sedation intra-operative with respiratory depression.

Study by Hunt c et al(10), showed a dose as low as 6.25mcg was sufficient to prolong spinal anesthesia. Patients who received doses of 12.5mcg and 25mcg displayed a trend towards lower post operative analgesia requirement but not of statistical significance. Patients receiving>/= 25mcg experienced troublesome pruritis.

Similar studies seem to indicate, in order to maximize post operative analgesia whilst minimizing respiratory depression and pruritis, a dose of 20mcg would appear optimal.

Preservative free Midazolam in 2mg dose was selected since this dose of midazolam, has been found safe and effective for analgesia. Safety of neuraxial administration of midazolam in human beings has been demonstrated by several investigations.

In our pilot studies plain hyperbaric bupivacaine was used in doses of 15mg(3cc), 17.5mg(3.5cc) and 20mg (4cc) , it was found that minimum of 17.5mg(3.5cc) of the drug was required for effective surgical anesthesia.

120 ASA I/II patients who were to undergo gynecological surgeries with expected duration of 2-2.5 hours under spinal anesthesia were randomly divided into 3 groups of 40 patients each.

The Fentanyl (F) Group I- 17.5mg of heavy bupivacaine +20mcg fentanyl/ total intrathecal volume of 3.9ml

The Midazolam (M) Group II- 17.5mg heavy bupivacaine + 2 mg preservative free midazolam/ total intrathecal volume of 3.9ml.

The Control (C) Group III- 17.5mg heavy bupivacaine + 0.4 ml sterile Normal saline/ total intrathecal volume of 3.9ml.These groups were compared for onset of block, hemodynamic stability, duration of block, post operative analgesia, analgesics over 24 hours and any possible adverse effects.

All three groups were comparable in terms of demographic variables like mean age, weight, height and ASA status. The surgeries carried out in the three groups are comparable with respect to Abdominal and vaginal approach

Addition of intrathecal fentanyl significantly reduced the time required to achieve maximum sensory block 6.76±0.51min as compared to 8.29±0.48 min $p<0.05$ in control group. And for motor block 7.20±0.65 min in fentanyl group compared to 8.31±0.44min $p<0.05$ in control group.

With Addition of Midazolam there was no clinical as well statistical difference with respect to Motor and sensory block as compared to Control group.

Fentanyl group achieved higher sensory dermatomal levels 35% in fentanyl group level T4-T5 as compared to 7.5% in control group and 12.5% in midazolam group.

Sensory levels of T4-5 was achieved in 35% in fentanyl group(highest in all the groups) all the patients had minimum level of T6-7.

Data confirmed by Adkisson (11) who demonstrated increased spread of spinal block with the addition of intrathecal fentanyl.

A study by Shende D (12) showed reduced time required to achieve desired sensory level though not statistically significant. Ephedrine was required earlier in Fentanyl group suggesting more rapid onset of sympathetic blockade in patients receiving intrathecal fentanyl.

Other studies referred to by us have not commented on the onset of spinal anesthesia after midazolam intrathecal (13)

Due to lipophilic nature, fentanyl does not spread rostrally in CSF, but moves rapidly from the CSF to the spinal cord and has rapid vascular uptake from the site of its intrathecal deposition leading to rapid onset of action(9). No such synergistic action with Local anesthetics has been demonstrated with the use of Midazolam.

None of the patients in either groups ever showed respiratory depression (Respiratory rate<12). There was no fall in SPO2 significantly above/below baseline in all the three groups.

Patients receiving intrathecal fentanyl had lower pulse rates both clinically and statistically for the intra and post operative period until upto 6 hours. After that it was not clinically significant only statistically. In patients receiving intrathecal midazolam the pulse rate was comparable with control group at all times except 2-5 hours where it was statistically lower but clinically not significant. None of the patients in either of the group had bradycardia both during intraoperative and post operative period.

Within 10 mins of intrathecal injection there was fall in blood pressure in the study group significant both clinically and statistically. This trend continued for 4 hours. After that though statistically lower systolic blood pressure was observed, it was not clinically significant.

2 patients (5%) in fentanyl group had hypotension systolic BP<20% of baseline within 30 mins of intrathecal injection, corrected with IV fluids. No further treatment was required and blood pressure was stable. None of the patients in either of the three groups required perioperative transfusion.

This indicates that intrathecal fentanyl 20 mcg and midazolam 2 mg do not produce respiratory depression and are hemodynamically stable. These results are in accordance to Catherine Hunt (10) and Shende D (12) for Fentanyl. similarly confirmed in studies for Midazolam by Batra YK (5), A Rudra (14) and D Bhattacharya (13).

The Sympathetic block along with higher levels of dermatomal block could explain for the persistently lower pulse rate and settled blood pressure in patients receiving intrathecal fentanyl. Better comfort, lesser pulling sensation on peritoneum could also account for stable hemodynamic parameters in the study groups (fentanyl and Midazolam).

Belzarena (8) had evidence of respiratory depression with higher doses of 0.5mcg/kg and 0.75mcg/kg. we did not find any evidence of respiratory depression our dose was found approximately(0.4mcg/kg).

In present study time required for sensory block to regress by two segments was longer in (F) group(160.52±14.8 mins) and

in (M) group (160.52±13.34 min) as compared to (138.25±5.51) in © group.

The Mean duration of both Sensory block (regression to L5-S1) and Duration of Motor Block (Bromage scale 0) was higher in both Fentanyl and Midazolam group as compared to Control group. Chart above. Results in agreement to study By Belzarena S (8) and Shende D (12)and Hunt C(10). Batra YK(5). Time to void, evidence of urinary retention could not be studied in either of the groups, as all the patients were catheterized preoperatively and the catheter was removed on day 2 postoperatively.

Our findings of analgesia requirements in 24 hours in all three groups were comparable. Mean total analgesic dose was (2.25±0.43 doses) in control group compared to (2.27±0.45 doses) in fentanyl group and (2.3 ±).516) in midazolam group. The studies we referred to had similar findings that only Immediate postoperative period had advantage of 1 to 1.5 hours pain free period the overall 24 hours requirement was comparable.

We also studied, the analgesic requirements in surgeries by two different approaches (Abdominal and Vaginal). It was postulated that surgeries with Vaginal approach would require less analgesic. In our study patients requiring 3 doses of analgesics were more in the abdominal Group 915% Fentanyl group, 30% in midazolam Group, 25% control group) than the vaginal group (12.5% Fentanyl group, 2.5% in midazolam group and none in control group. Pain during these abdominal surgical procedures is mainly of visceral origin, relief of which is superior with narcotics. Midazolam is thought to be more useful in reliving somatic pain than visceral pain **(13,14).** Fentanyl being opioid can be preferred over midazolam for visceral pin relief. Also duration of both sensory and motor blockade was longer in fentanyl group. None of the literature has studied the analgesic requirements according to routes of surgery. No intergroup difference was found the study.

Our study has nausea and vomiting 22.5% in F group, 5% in M group and 12.5% in C group. This was in contradiction to findings of Dahlegran (15)who reported decrease incidence of nausea and vomiting. Postulation could be opioid effect.

PDPH in 1 patient settled with head low /IV Fluids /analgesics Shivering was found in 10% of M group and 15% in C group and none in F group settled with warm IV fluids/ blankets and Ondansetron 4 mg

2 patients in midazolam group had to be given General anesthesia at 3 hours as they did not allow surgery after 3 hours and hence were excluded from study after 3 hours.

None of the patients in either groups had adverse effects like high spinal block, pruritis etc. None of the patients experienced Transient neurological symptoms.

CONCLUSION:

Of the many intrathecal adjuvants, we studied fentanyl and midazolam when used in gynecological surgeries. Use of both these drugs have shown to increase intraoperative comfort and postoperative analgesia

Our results show that hemodynamic parameters, pulse rate and blood pressure are well maintained throughout the intra and postoperative period. No patient showed evidence of respiratory depression. Onset of sensory level was fast in the group with intrathecal fentanyl as compared to the other two groups.

The time required for two segment egression and the duration of sensory and motor blockade was also prolonged in both fentanyl and Midazolam group as compared to control group. Intraoperatively patients in both the fentanyl and midazolam group were sedated as compared to the control group.

The duration of analgesia was increased postoperatively by not more than 1 to 1.5 hours in Fentanyl and midazolam group as compared to Control group.

The 24 hour analgesic requirement in all three groups was comparable. These intrathecal additives did not change the analgesic requirements in 24 hours.

Intraoperative nausea and vomiting was higher in fentanyl group, shivering common in midazolam group.

From the present study we conclude that intrathecal addition of both Fentanyl citrate 20mcg to heavy bupivacaine and 2mg of preservative free midazolam to heavy bupivacaine is safe and hemodynamically stable for the patients. Fentanyl has the advantage of significantly prolonging duration of motor and sensory blockade. It appears to be useful in abdominal surgery, of which visceral pain is predominant component.

The postoperative pain relief is increased by duration of 1 to 1.5hours. Both the drugs do not decrease the 24hours analgesic requirement as compared to bupivacaine alone.

Therefore for prolonged postoperative pain relief epidural route of analgesia or other longer acting adjuvants could be considered.

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