COMPARISON OF INTRATHECALLY ADMINISTERED FENTANYL AND MIDAZOLAM IN COMBINATION WITH HYPERBARIC BUPIVACAINE
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ABSTRACT: To evaluate and compare the efficacy of intrathecally administered midazolam and fentanyl in combination with hyperbaric bupivacaine with respect to, the time of onset, duration of sensory block, Quality of intraoperative anesthesia, duration of effective postoperative analgesia, incidence of side effects. Regional anaesthesia techniques provide an excellent means for managing postoperative pain. Various adjuvants has been added to spinal local anaesthetic to prolong postoperative analgesia. The purpose of the study is to compare the efficacy of intrathecally administered hyperbaric bupivacaine with fentanyl and midazolam in terms of onset of sensory block, Intraoperative comfort and postoperative analgesia

KEYWORDS: Opioids, Anaesthetics, Antagonism, Postoperative Analgesia, Fentanyl and Midazolam.

INTRODUCTION: Pain is a fundamental biological phenomenon. Pain is always underestimated and under treated. The relief of pain during surgery is the main part of anaesthesia.

Pain is derived from latin word 'poena' which means penalty or punishment.¹ The most important duty of an anesthesiologist lies in providing relief from pain throughout the intraoperative period. Extending the pain relief into the post-operative period is necessary for both physiological and psychological well-being of the patient². Understanding pain is essential to achieve both these goals.³

The spinal cord has taken the centre stage in analgesia practice following the demonstration of analgesia with intrathecal morphine by Yaksh and Rudy (1977).⁴ Deposition of drugs in the subarachnoid space and epidural space paved a new era for pain relief.

Regional anesthetic techniques provide an excellent means for managing postoperative pain following elective anesthesia of the lower half of the body. Spinal anesthesia with bupivacaine provides effective analgesia in the early postoperative period (Kim and Lee, 2001).⁵

Various adjuvants have been added to spinal local anesthetic to prolong postoperative analgesia. Intrathecal opioids provide effective postoperative analgesia but are associated with adverse effects such as itching, nausea, urinary retention, sedation, ileus and life-threatening respiratory depression⁶ have prompted further research to develop non opioid analgesics with less side effects.⁷ Other adjuvants such as clonidine and ketamine have also been administered but none have become established in regular clinical use because of their adverse effects (Whiting, 2003).
Intrathecal midazolam has been reported to have antinociceptive action. Evidence indicates that intrathecal midazolam may be useful in the treatment of somatic pain. Recent studies have also shown that midazolam produces an analgesic action through the benzodiazepine gamma amino butyric acid (GABA) receptor complex in the spinal cord (Tucker et al., 2004).8

Present study is for comparing the efficacy of midzolam and fentanyl when administered intrathecally in association with bupivacaine.

MATERIALS AND METHODS: A prospective, randomized and single blind study was carried out to study the effect of fentanyl and preservative free midazolam to intrathecal hyperbaric bupivacaine in patients undergoing elective lower abdominal surgeries at S.V.R.R.G.G.H, Tirupati after Informed consent was obtained from the patient. It was approved by Institutional Ethical committee, S.V.M.C. The study was conducted in 120 patients posted for elective surgeries in S.V.R.R.G.G.H, Tirupati.

Inclusion Criteria: Adult patients aged 18-60yrs, ASA physical status I and II, Both genders, Surgeries on the lower half of the body (Hernia repair, Perineal Operations as piles and Fissures, Lower limb orthopedic surgeries, Gynecological surgeries), Normal coagulation profile.

Exclusion Criteria: Patient refusal, ASA Grade III & IV, Morbid obesity, Pregnancy, Neuromuscular disorders, Thyroid disorders, Hepatic and renal diseases, Post burns, Known allergy to drugs, Patients who were converted to general anaesthesia.

Patients were grouped into three groups Group B, Group M and Group F. Each group has 40 patients. All the patients received injection Atropine 0.6 mg intramuscularly 45 minutes before induction.

Group B: Received 15mg of 0.5% hyperbaric bupivacaine and 0.5ml of 0.9% sodium chloride solution.

Group M: Received 15mg of 0.5% hyperbaric bupivacaine and 1mg (0.2ml) of preservative free midazolam and 0.3 ml of 0.9% Sodium chloride solution.

Group F: Received 15 mg of 0.5 hyperbaric bupivacaine and 25mcg (0.5ml) of fentanyl. Total drug volume in all the three groups is 3.5ml

PROCEDURE: All the patients were thoroughly examined in the pre-anaesthetic checkup, patients having neurological, cardiovascular, and respiratory, coagulation disorders and other system disorders, hypotension, emotional instability, unwillingness and any anticipated difficulty in regional anaesthesia were excluded. The procedure was thoroughly explained to the patient and informed consent was taken from them.

INVESTIGATIONS: Routine laboratory investigations like Hb%, TC, DC, ESR, PCV, BT, CT, Blood grouping and typing, Blood sugar, blood urea, serum creatinine, urine for albumin and sugar, screening and microscopic examination were done. ECG was also taken.
TECHNIQUE AND MANAGEMENT: Base line pulse rate, blood pressure and respiratory rate were recorded. Intravenous line was secured with 18 G canula. Preloading was done with 15-20ml / kg of crystalloid solution. Emergency drugs and equipment were kept ready.

Patients were put on right lateral position, under strict aseptic precaution. Subarachnoid block was performed using 23G Quinke Babcock`s needle in L3 – L4 interspaces. After ensuring free flow of CSF the drug was injected as per the group assigned. After injecting the drug patients were turned supine.

RECORDING DATA: The following were recorded

1. Time of injection of subarachnoid block.
2. Maximum level of sensory block achieved (which is tested by pinprick).
3. Time of onset of the maximum level of sensory block.
4. Time of onset of the of surgery.
5. Pulse rate, blood pressure, respiratory rate and oxygen saturation were monitored every 5 minutes for the first 15 minutes, there after every 10 minutes for rest of the surgery and every half an hour in the post-operative period.
6. Hypotension was said to have occurred, if there was a fall in blood pressure 25% from the baseline. This was treated with 100% oxygen through face mask, intravenous fluids and mephentermine intravenously at 6 mg increments. Bradycardia was treated by inj.atropine 0.6 mg IV, rapid infusion of intravenous fluids.
7. Nausea and Vomiting were treated with inj. ondensetron 4 g IV, Shivering was treated with warms drapes and warm intravenous fluids.
8. The quality of intraoperative analgesia was evaluated by the patient at 30 minutes intervals using the following 4 point scale.
   a. Excellent analgesia, no sensation at all from the surgical site.
   b. Adequate analgesia, sensation of motion only.
   c. Inadequate analgesia, discomfort, but the patient declines additional analgesia.
   d. Major discomfort, addition analgesics are required.
9. Occurrence of pruritus was noted.
10. Two segment regression time i.e., the time taken to decrease from maximum sensory level by two segment from the initial level noted.
11. Analgesia: Pain in the post-operative period was evaluated using visual analogue scale.

|   |   |
|---|---|
| 0 | No pain |
| 2 | Mild pain |
| 4 | Moderate pain |
| 6 | Severe pain |
| 8 | Very severe pain |
| 10 | Worst possible pain |

Supplementary analgesia was given if the patient developed moderate pain (VAS 4) during the post-operative period. The duration of analgesia was taken as the time between the institution of subarachnoid block and analgesic requirement.
12. In the post-operative period patients were followed up for any complication like respiratory depression, post-operative nausea and vomiting. The statistical significance was brought by student ‘t’ test. Chi square test was used to see the association between groups for categorical variables. All statistical analysis was done by using SPSS (Statistical Packages for Social Sciences, Chicago) 11.5 Software.

DISCUSSION: The international Association and Society for Pain (IASP) defines pain as "An unpleasant sensation and emotional experience associated with actual or potential tissue damage or described in terms of such damage."9

It has also been defined by Sherington in 1906 as "The physical adjunct of protective reflex".

The gate control theory10 of pain has considerable influence on the anaesthesiologists’ management of pain focusing attention on the unique pharmacology of the dorsal horn of the spinal cord. The technique has implication in acute and chronic pain therapy. A typically modern view of perioperative pain is to view it as an impediment to recovery. Aggressive methods are often used to minimize pain to facilitate hospital discharge and a rapid return to normal functional activity.

Opioids have been used for pain relief since time immemorial and are still considered the gold standard analgesic medication. The advances in pain relief with opioids include the discovery of newer drugs and the use of various routes of administration of the drug. In addition to the conventional oral, sublingual, intramuscular and intravenous routes opioids and benzodiazepines are also administered into the central neuraxis. The neuraxial adjuvants like opioids and benzodiazepines are becoming increasingly popular because of their prolonged duration of action, minimal incidence of side effects and good intraoperative comfort.

Spinal anesthesia continues to be the commonly used anesthetic technique in our country. Hence the addition of the adjuvants to the local anaesthetic becomes easier.

To address the problem of limited duration of action and to improve the quality of analgesia both intraoperative and postoperative, intrathecal opioids have been given in addition to bupivacaine. In 1979, Wang and others reported11 the first use of intrathecal morphine in patients with intractable pain.

Among the opioids, lipophilic drugs are safer within the central neuraxis as their cephalad spread is restricted. On administration into the CSF, the opioid gets attached to the spinal cord opioid receptor and produce their effect. Among the benzodiazepines, only the midazolam is used within central neuraxis. It produces analgesia by binding to the specific benzodiazepine receptor in the dorsal horn of the spinal cord.

In our clinical study, 120 patients in the age group between 18- 60 years posted for various elective lower abdominal surgeries belonging to ASA physical status I and II were selected. Patients are grouped into three groups Group B, Group M and Group F. Each group has 40 patients.

Group B: Received 15mg of 0.5% hyperbaric bupivacaine and 0.5ml of 0.9% sodium chloride solution.
Group M: Received 15mg of 0.5% hyperbaric bupivacaine and 1mg (0.2ml) of preservative free midazolam and 0.3 ml of 0.9% Sodium chloride solution.

Group F: Received 15 mg of 0.5 hyperbaric bupivacaine and 25mcg (0.5ml) of fentanyl.

Total drug volume in all the three groups is 3.5ml.

The present study has found that there were no statistically significant differences in terms of demographic properties, ASA grading, the mean age, weight and gender of patients and were comparable in all the three groups.

Major advantages have been observed with following parameters.

1. **Time of onset of sensory block:** In the present study the time required to achieve the maximum level of block has been shortened with the addition of midazolam and fentanyl but more so with fentanyl. The p value for time of onset is found to be,
   - 0.0001 on comparing group B and group M.
   - 0.00001 on comparing group B and group F.
   - 0.013 on comparing group M and group F.
   
   Since p value is less than 0.05, this faster onset of action is found to be statistically significant.

2. **Two segment regression time:** The two segment regression time is prolonged in both adjuvant groups compared with the control group in a statistically significant manner. The p value for two segment regression time is found to be,
   - 0.0001 on comparing group B and group M.
   - 0.000001 on comparing group B and group F.
   - 0.00001 on comparing group M and group F.

3. **Duration of analgesia:** Duration of analgesia has been shown to be prolonged with the addition of the midazolam and fentanyl. Fentanyl scores over midazolam in duration of analgesia in a statistically significant manner. The p value has been found to be,
   - 0.0001 on comparing group B and group M.
   - 0.000001 on comparing group B and group F.
   - 0.00001 on comparing group M and group F.

| Groups | Time of onset (Minutes) | Two segment regression time (Minutes) | Duration of analgesia (Minutes) |
|--------|-------------------------|--------------------------------------|--------------------------------|
| B      | 7.35±1.33               | 96.28±17.84                          | 145.55±16.69                   |
| M      | 4.55±1.28               | 141.63±15.87                         | 195.08±19.72                   |
| F      | 4.03±0.97               | 190.75±18.18                         | 253.63±26.79                   |
| Comparison |               |                                      |                                |
| B and M | 8.31                  | 9.81                                | 14.2                           |
| P      | 0.0001                 | 0.0001                              | 0.0001                         |
### OBSERVATION AND RESULTS:

All the three groups (Group B, Group M, Group F) are compared in different terms and the data is presented as mean ± standard deviation. ‘t’ test and ‘p’ value are selected for eliciting the significance of difference between the three groups.

P value < 0.05 was considered as statistically significant.

#### Demographic data:

| Sl. No. | Group | Age (Mean ± SD) | ‘t’ value & ‘p’ value |
|---------|-------|-----------------|-----------------------|
| 1       | B     | 42.3±10.52      | B vs M t = 1.02; p = 0.31; NS |
| 2       | M     | 40.0±10.08      | B vs F t = 1.02; p = 0.31; NS |
| 3       | F     | 39.1±9.84       | M vs F t = 1.02; p = 0.31; NS |

Table 1: Mean age comparison among the three groups

As ‘p’ value is > 0.05 when compared, there is no significance difference among these three groups.

| Group | %    |
|-------|------|
| Male  | 62.5 |
| Female| 37.5 |

Table 2: Sex Distribution

| Sl. No. | Group | Weight (Mean±SD) | “t” value & “p” value |
|---------|-------|------------------|-----------------------|
| 1       | B     | 59.6±5.27        | B vs M t=1.89 p=0.06 NS |
| 2       | M     | 56.5±6.06        | B vs F t=1.24 p=0.21 NS |
| 3       | F     | 57.5±4.76        | M vs F t=0.88 p=0.38 NS |

Table 3: Mean weight comparison among the groups

Data presented as Mean±SD. The mean weight of three groups when compared among them there is no significant difference.

| Sl. No. | Group | PR (Mean±SD) | ‘t’ value & ‘p’ value |
|---------|-------|--------------|-----------------------|
| 1       | B     | 73.3±11.06   | B vs M t = 1.35; p = 0.18; NS |
| 2       | M     | 76.3±9.13    | B vs F t = 1.64; p = 0.10; NS |
| 3       | F     | 76.8±7.94    | M vs F t = 0.25; p = 0.80; NS |

Table 4: Mean pulse rate comparison among the groups

There is no significant difference in baseline pulse rate among the groups.
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### Table 5: Mean SBP comparison among the groups

| Sl. No. | Group | SBP (Mean±S.D) | ‘t’ value & ‘p’ value |
|---------|-------|----------------|-----------------------|
| 1.      | B     | 118.6±8.30     | B vs M t = 0.09; p = 0.92; NS |
| 2.      | M     | 118.8±11.05    | B vs F t = 1.14; p = 0.26; NS |
| 3.      | F     | 120.7±8.21     | M vs F t = 0.87; p = 0.38; NS |

### Table 6: Mean DBP comparison among the groups

| Sl. No. | Group | DBP (Mean±S.D) | ‘t’ value & ‘p’ value |
|---------|-------|----------------|-----------------------|
| 1.      | B     | 68.1±3.32      | B vs M t = 1.83; p = 0.07; NS |
| 2.      | M     | 70.5±7.59      | B vs F t = 1.38; p = 0.17; NS |
| 3.      | F     | 69.4±4.69      | M vs F t = 0.77; p = 0.43; NS |

### TIME OF ONSET OF MAXIMUM LEVEL OF SENSORY BLOCK:

| Sl. No. | Group | Onset (Mean±S.D) | ‘t’ value & ‘p’ value |
|---------|-------|------------------|-----------------------|
| 1.      | B     | 7.28±1.18        | B vs M t = 8.31; p <0.001; S |
| 2.      | M     | 4.80±1.47        | B vs M t = 13.40; p <0.001; S |
| 3.      | F     | 4.10±0.93        | B vs M t = 2.55; p = 0.013; S |

### Table 7: The time taken to reach the maximum sensory level

Data presented as Mean± S.D. The mean onset of sensory block in group B is 7.28±1.18, in group M is 4.80±1.47 and in group F is 4.10±0.93 and ‘P’ value is <0.05; hence there is significant time difference in reaching maximum sensory level among the three groups.

It is the interval between time of maximum onset of sensory block to the time of regression in upper two segments.

### Table 8: Two segment regression time

| Sl. No. | Group | Two segment regression time (Mean±SD) | ‘t’ value & ‘p’ value |
|---------|-------|--------------------------------------|-----------------------|
| 1.      | B     | 98.1±19.83                          | B vs M t = 9.81; p <0.001; S |
| 2.      | M     | 138.3±16.62                         | B vs F t = 16.7; p <0.001; S |
| 3.      | F     | 190.8±28.88                         | M vs F t = 9.96; p <0.001; S |

Data presented as mean±S.D.The mean duration of two segment regression time in group B is 98.1±19.83, in group M is 138.3±16.62 and in group F is 190.8±28.88 and ‘p’ value is <0.05; hence there is significant difference in two segment regression time among the three groups.

The duration of analgesia was taken as the time between the injection of subarachnoid block and analgesic requirement.
### Table 9: Duration of analgesia

| Sl. No. | Group | Duration of Analgesia (Mean ± SD) | ‘t’ value & ‘p’ value |
|---------|-------|----------------------------------|----------------------|
| 1.      | B     | 141.1±16.27                      | B vs M t = 14.2; p < 0.001; S |
| 2.      | M     | 193.8±16.90                      | B vs F t = 20.5; p < 0.001; S |
| 3.      | F     | 251.8±30.10                      | M vs F t = 10.6; p < 0.001; S |

Data presented as mean±S.D. The mean duration of analgesia in group B is 141.1±16.27, in group M is 193.8±16.90 and in group F is 251.8±30.10 and ‘p’ value of mean duration of analgesia when compared among the three groups it is <0.05; hence there is a significant difference among the groups.

### Table 10: Side Effects

| Side effect             | Group B | Group M | Group F |
|-------------------------|---------|---------|---------|
| Hypotension             | 3       | 3       | 6       |
| Bradycardia             | 3       | 2       | 4       |
| Respiratory depression  | 0       | 0       | 1       |
| Nausea & vomiting       | 2       | 2       | 4       |

### CONCLUSION:
From this study comparing the midazolam and fentanyl in intrathecal administration shows that, the addition of fentanyl and midazolam gives better intraoperative comfort and postoperative analgesia than local anaesthetic bupivacaine. But the fentanyl gives more comfort and prolonged duration of analgesia than midazolam. The midazolam gives more hemodynamic stability than fentanyl group, by fewer incidences of hypotension and bradycardia. The sedation without desaturation is a welcome effect in the immediate post-operative period with midazolam.

### REFERENCES:
1. Larson MD. History of anaesthesia practice; Chapter 1 in Miller’s Anaesthesia, Sixth edition, Elsiever Churchill Livingstone, 2004; 3- 54.
2. Vaswani RK, Raiger LK, Purohit R et al; The effect of intrathecal midazolam on postoperative pain relief in orthopaedic surgery. Hospital Today 2002; 7 (4): 150 – 153.
3. Howard L Fields, Joseph B Martin; Pain pathophysiology and management in Harrisons principles of Internal Medicine, 15 th edition, MC Grewhill, 2001.
4. Yaksh T, Rudit, Analgesia mediated by a direct spinal action of narcotics, science 1976; 192: 1351– 1358.
5. Kim MH, Lee YM. Intrathacal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing hemorrhoidectomy.Br J Anaesth 2001; 86: 77-90.
6. Eisenach JC. Overview; First International Symposium on alpha -2 adrenergic mechanisms of spinal anaesthesia. Reg. Anaesth, 1993; 18 (4s); i – iv 7.
7. Dobrydrijov I, Samartiel J. Enhancememnt of intrathecal lidocaine by addition of local and systemic clonidine. Acta Anaesthesiol Scand, 1999; 43: 556- 62.

8. Tucker AP, Mezzatesta J, Nadeson et al; Intrathecal midazolam II: Combination with intrathecal fentanyl for labour pain. Anaeath Analog 2004 Jun; 98 (6): 1521 – 7.

9. A sample list of frequently used terms. International Association for the Study of Pain Task Force on Taxonomy. In: Merskey NB, ed. Classification of Chronic Pain, 2nd ed. Seattle: IASP Press; 1994: 209-214.

10. Melzaek R, Wall PD. Pain mechanisms: A new theory. Science.1965 Nov 19; 150 (3699): 971 – 979.

11. Wang Jetal, Pain relieved by intrathecally administered morphine in men, Anaesthesiology, 1979; 50: 149 – 181.

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