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PUBLISHED PAPER'S TITLE : ANALGESIC EFFICACY OF INTRATHECAL MIDAZOLAM WITH BUPIVACAINE IN PATIENTS UNDERGOING TRANSURETHRAL RESECTION OF PROSTATE

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Research Paper

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ANALGESIC EFFICACY OF INTRATHECAL MIDAZOLAM WITH BUPIVACAINE IN PATIENTS UNDERGOING TRANSURETHRAL RESECTION OF PROSTATE

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Declaration

The Declaration of the authors for publication of Research Paper in Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772) We Dr. Indrajit Kumar1,Dr.shashi prakash2,prof.R K Verma3,Dr.sandeep khuba2,Dr A K Paswan2, and Prof.U S Dwivedi4 the authors of the research paper entitled ANALGESIC EFFICACY OF INTRATHECAL MIDAZOLAM WITH BUPIVACAINE IN PATIENTS UNDERGOING TRANSURETHRAL RESECTION OF PROSTATE declare that , We take the responsibility of the content and material of our paper as We ourself have written it and also have read the manuscript of our paper carefully. Also, We hereby give our consent to publish our paper in ajmams , This research paper is our original work and no part of it or it's similar version is published or has been sent for publication anywhere else.We authorise the Editorial Board of the Journal to modify and edit the manuscript. We also give our consent to the publisher of ajmams to own the copyright of our research paper.

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Background : The present study was undertaken to evaluate the safety and efficacy of addition of Medazolam to bupivacaine to compare it with hyperbaric bupivacaine in patient undergoing transurethral resection of prostate and also compare there haemodynamic effect and side effect any.

Material and Method : A total of 40 patients belonging ASA Gr I and II presenting for transurethral resection of prostate where included in this study. The patients were randomly allocated one of the two groups of 20 each. Group – B : 20 patients received hyperbaric bupivacaine 0.5% (H) 1.5ml (control group);
Group MB : 20 patients received 1.5ml bupivacaine + 1.5ml Medazolam intrathecally.
(HR) Heart rate, mean arterial pressure (MAP), Pulse Oximeter (SPO_2), Respiratory rate (RR) were observed and recorded throughout the study period at regular interval and also observed side effect of each group.

Result : The addition of 1.5mg of Midazolam to hyperbaric bupivacaine when given intrathecally improved the duration of sensory block. Our results are consistent with

experimental effects of intrathecal midazolam which shows that combination of midazolam and bupivacaine are synergistic effect without any adverse effects.

Conclusions : Adding of 1.5mg midazolam to 1.5ml of hyperbaric bupivacaine in spinal anaesthesia for trans urethral resection of prostate surgery.
Enhance the efficacy of bupivacaine hyperbaric by prolonging the duration of sensory block without prolonged motor recovery. It also provided sedation intraoperatively. There was no significant difference in the haemodynamic changes between all group. No significant side effect were noted in between both groups. Prolonged analgesic efficacy noted in it of group II (MB) as compare to group I(B).

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Key words - *Transurethral resection of prostate, Midazolam, Bupivacaine, Spinal Anaesthesia*

INTRODUCTION

Use of spinal anaesthesia for surgical procedures in very common in our country. This may be because of economic reasons and lack of availability of sophisticated anaesthetic apparatus and gases in rural and semi-urban areas where a majority of our population resides.

Since the introduction of hyperbaric solution for spinal anaesthesia by Barker (1907), the, choice has been more in favour of this type of solution. In this country, for some time past, spinal anaesthesia was being induced almost invariably with lignocaine in 7.5% dextrose as this was the only available solution for this purpose in the market. Though heavy lignocaine has many advantages, the main disadvantage is its short duration of action (about 60 min) which proves inadequate for many types of operations.

Bupivacaine, a longer acting local anesthetic agent was synthesized in the year 1957 by Eckenstam and was first used clinically by Telivuo in the year 1963. It has a considerably long duration of action (Telivuo, 1963; Widman, 1964; Ekblom and widman, 1966).

Although bupivacaine was introduced initially, to be used as an hyperbaric solution for spinal anaesthesia (Ekblom and Widman, 1966), it was shown later that the isobaric solution (glucose free solution or plain solution) is also useful in spinal anaesthesia (Notle et al., 1977; Lanz, Schellenberg and Theiss, 1979, Cameron et al., 1981).

Workers like Louthan et al. (1965), Henschel et al. (1967) and Wildsmith et al. (1981) were of the opinion that the Isobaric bupivacaine has advantages over the hyperbaric solution in certain types of operations as the spread of anaesthesia is not influenced by the position of the patient.

Transurethral resection of benign hypertrophy of the prostate gland or of bladder tumour contributes a high percentage of the workload of urological surgery. Both the pathological conditions involved occur predominantly in the elderly and therefore a high incidence of other pathology can be expected.

The aim of this study is to compare the

1. Efficacy and safety of addition of midazolam 1.5 mg to bupivacaine
2. Their Heamodynamic effects.
3. Side effects, if any
4.

MATERIAL AND METHODS

The present study was undertaken to evaluate the safety and efficacy of addition of midazolam to bupivacaine to compare it with hyperbaric bupivacaine. In patients undergoing transurethral resection of prostate.

A total of 40 patients belonging to ASA grade I and II presenting for transurethral resection of prostate were included in this study. The patients were randomly allocated one of the two groups of 20 each. The study groups according to anaesthetic solution used were as follows.

Group B – 20 patients received hyperbaric bupivacaine 0.5% (H) 1.5ml (control group)
Group MB – 20 patients received 1.5 ml hyperbaric bupivacaine 1.5mg midazolam
intrathecally

All the patients were premedicated with tab alprazolam 0.5 mg in the night the day before surgery and in the morning on the day of surgery.

ECG, noninvasive blood pressure and peripheral oxygen saturation were monitored. Before lumbar puncture, intravenous access was secured with 18 gauge intravenous cannula and an infusion of normal saline 0.9% was started. Spinal anesthesia was performed at L_{3-4} or L_{4-5} interspace in lateral decubitus position.

HEMODYNAMIC PARAMETERS

Once the patients were made to lie supine, pulse, noninvasive blood pressure were recorded every 3 min in first 15 min after spinal anesthetic and then every 5 min until the end of surgery. Hypotension (SAP < 90 or 30% decrease from baseline) and bradycardia (HR<45) were treated with IV bolus of ephedrine 5mg and atropine 0.6mg IV respectively.

The cephalad spread of analgesic (loss of sensation to pinprick) was determined with a blunt 24G needle at intervals specified above. The highest dermatome level, time to reach this level and 2 segment regression was recorded.

MOTOR BLOCKADE (BROMAGE SCALE)

The degree of motor blockade was assessed with Bromage scale and the degree of sedation was assessed by Ramsay Sedation Score.

I	Fully awake
II	Drowsy
III	Sleeping comfortably but arousable to verbal commands
IV	Deep sleep, but arousable to mild physical stimulus
V	Deep sleep, not arousable

ADVERSE EFFECTS

Side effects like nausea, vomiting, respiratory depression, bronchospasm, pruritis, urinary retention neurological symptoms and hiccoughs were observed in subjects of all the groups.

VISUAL ANALOGUES SCORE (VAS SCORE)

0	10
(No pain)	(Severe pain)

Visual analogous scale (VAS) of 0-10 cm (with 0=no pain and 10= severe pain) recommended by Scott and Huskinson at regular interval. A slide rule marker was sued at regular interval of postoperative visit to assess the level of pain.

OBSERVATION & RESULTS

A total 40 patients in the age group 50-60 yrs of age belonging to ASA grade I and II were included in the study. These patients were divided into two groups, each group comprising of 20 patients. Patients in group B we given 1.5 ml hyperbaric bupivacaine only intrathecally in L_{3-4} interspace while patients in group BM, 1.5 ml hyperbaric bupivacaine + 1.5mg midazolam was given.

Patients in both the group were compare with each other regard to onset of sensory block at level T_{10} and onset of motor block, pulse rate, oxygen saturation, mean blood pressure, sedation and adverse effect such as nausea, vomiting pruritus, respiratory depression, urinary retention and hiccough.

SENSORY BLOCK

The mean onset and duration of pain relief in these groups is shown in table 1. Mean time of onset of sensory block at T_{10} level was at 2.37±0.15 minutes in group B while in group BM the sensory level of T_{10} was achieved at 2.29±0.12 minutes as shown in table 1. There was no statistically significant difference in the onset block between both groups. Duration of sensory block was prolonged with addition of midazolam. Means duration of block was prolonged in group BM. Mean duration of pain relief in group **B** patients was 60.15±2.87 minutes while in group BM was 89.75±4.70 minutes. This difference in the mean duration of pain relief was highly significant ($p < 0.001$).

There were no significant differences in onset of motor block with addition of midazolam as shown in table 1. Bromage scale III was achieved in group B subjects at 2.14±0.18 minutes, while in group BM was 2.01±0.25 minutes. The difference in onset time and duration of motor block was not statistically significant in the two groups.

Statistical comparison of mean pulse rate between group B and group BM at different time intervals (minutes) are shown in table 2. there was significant variation in pulse rate between all two groups. The difference was highly significant after 45 minutes of injecting the study solution intrathecally ($P<0.001$) in both groups. The variation in pulse rate with in group B was significant till 45 minutes and then started declining.

Mean pulse rate in group B and group BM at different time intervals and the statistical comparison between groups in shown in table 2. The variation in pulse rate between group B and group BM was insignificant.

Changes in mean arterial pressure in group B and group BM at different time intervals are shown in table 3. There was a significantly fall in mean arterial pressure in group B but in group BM mean arterial pressure more stable.

Mean oxygen saturation of group B and group BM at different time intervals is shown in table 4. The oxygen saturation decrease significantly as compared to the mean initial value from 15 to 45 minutes in group BM only.

There was no significant difference in mean oxygen saturation at different time intervals between the two groups.

Sedation in all groups was assessed with Ramsay sedation score.

In group BM most of the patients were drowsy after 10 minutes of injecting the study solution and 90% of the patients got sedated with a sedation score of 2 after 15 minutes. This sedation lasted for 30-45 minutes. At 60 minutes, all the patients were fully awake with a sedation score zero. In group B, all the patients were fully awake through out the operation with a sedation score of zero. None of the patients in both groups received any intravenous sedation intraoperatively.

The five (25%) cases in group B had hypotension as compared to group BM, Three (15%). The hypotension was managed by injecting mephentemine (5 to 10mg) intravenous. The incidence of hypotension in group B was statistically significant ($p<0.05$) as compare to group BM.

The incidence of hypoxia / respiratory depression was two (10%) in group BM as compared to one (10%) in group B. However there is no statically significant difference in incidence among two groups. The incidence of nausea and vomiting was no significant (>0.05) in both the groups.

Table 1 : Mean age in two groups and their statistical in any group

	Group B	**Group BM**	**t value**	**p value**
Age	52.32 ± 7.86	54.23 ± 5.69	1.736	> 0.05
Height (cm)	162.10 ± 20.09	155.22 ±10.26	1.3639	0.1806
Onset of sensory block (min)	2.37 ± 0.15	2.29 ± 0.12	1.86	> 0.05
Onset of motor block (min)	2.14 ± 0.18	2.01 ± 0.12	1.08	> 0.05
Onset of sensory block (min)	60.15 ± 2.37	80.75 ± 4.70	23.87	< 0.001
Duration of analgesia (min)	161.50 ± 31.20	230.00 ± 92.39	3.1414	< 0.01

Table 2 : Mean pulse rate between group B and group BM at different time intervals (Min)

Pulse rate (per minute)	**Group B (n=20)**	**Group BM (n=20)**	**t value**	**p value**
Base line	78.65 ± 5.56	77.40 ± 4.21	0.8016	0.4278
2	81.23 ± 4.87	80.50 ± 3.66	0.5359	0.5952
5	80.79 ± 4.93	80.90 ± 4.56	0.0733	0.9440
10	80.75 ± 7.36	79.90 ± 4.27	0.4467	0.6576
15	80.30 ± 6.13	78.70 ± 4.36	0.9512	0.3475

30	81.20 ± 7.63	79.10 ± 3.21	1.1345	0.2637
45	76.60 ± 5.98	77.20 ± 6.06	0.3152	0.7544
60	78.85 ± 9.05	78.60 ± 4.54	0.1104	0.9127

Table 3 : Mean arterial pressure (mmHg) in group B and group BM at Different time intervals (Min)

Mean arterial pressure at different time intervals	**Group B (n=20)**	**Group BM (n=20)**	**t value**	**p value**
Base line	90.36 ± 5.35	89.57 ± 5.48	0.4613	0.6472
2	89.95 ± 6.15	89.25 ± 4.66	0.4057	0.6872
5	88.45 ± 6.41	87.45 ± 4.66	0.5643	0.5759
10	88.85 ± 6.95	87.10 ± 3.94	0.9796	0.3335
15	88.15 ± 6.25	87.30 ± 6.64	0.4169	0.6791
30	89.35 ± 5.47	88.20 ± 5.38	0.6703	0.5067
45	89.25 ± 5.10	88.50 ± 5.02	0.4687	0.6420
60	89.60 ± 5.18	87.90 ± 5.75	0.9824	0.3321

Table 4 : Mean oxygen saturation in group B and group BM at different Time intervals (Min)

Oxygen saturation (Min)	**Group B (n=20)**	**Group BM (n=20)**	**t value**	**p value**
Base line	97.19 ± 1.68	97.23 ± 1.65	0.0760	0.9398
2	97.83 ± 2.15	97.63 ± 1.29	0.3567	0.7233
5	96.55 ± 2.89	97.15 ± 2.88	0.6577	0.5147
10	97.58 ± 1.59	97.05 ± 1.87	0.8563	0.3972
15	97.22 ± 1.48	97.58 ± 1.78	0.7048	0.4852
30	96.23 ± 2.53	97.63 ± 2.08	1.9616	0.0635
45	97.21 ± 1.57	97.31 ± 2.19	1.1660	0.8691
60	96.27 ± 1.66	96.54 ± 2.05	0.4578	0.6497

DISCUSSION

In order to increase the duration of intraoperative and post operative analgesia, a large number adjuvants have been added to spinal anaesthetics. The use of opoids in intrathecal or epidural anaesthesia has become popular to optimize post-operative analgesia. Low cost, ease of administration and effectiveness of epidural and spinal opiods makes then an attractive option. However, opiods induced side effects, such as sedation, nausea, vomiting, pruritis, urinary retention and the risk of delayed respiratory depression, have perhaps limited widespread use of these agents.

Benzodiazepines are widely used in medical practice, their potent sedative, myorelaxant, anticonvulsant and anxiolytic properties are well established. The effect of benzodiazepines on response to painful stimuli, are not well defined. They are not normally considered to be analgesics.

However, one may confine the action of benzodiazepines to the spinal cord by giving them intrathecally thus, allowing access to receptors that mediate analgesia, the measurement of which is not confused by changes in level of consciousness.

Our study demonstrates that the addition of 1.5 mg of midazolam to hyperbaric bupivacaine when given intrathecally improved the duration of sensory block. Our results are consistent with experimental effects of intrathecal midazolam which shows that combination of midazolam and bupivacaine are synergistric effect with out any adverse effects. Intrathecal midazolam provides analgesia that is clearly segmental and therefore spinally mediated. The segmental analgesia caused by midazolam is the result of combination of midazolam with benzodiazepine-GABA receptor complex in the spinal cord, proved by the antagonism of its action by benzodiazepine antagonist Flumazenil.

Midazolam induced analgesia is reversed by the opioids antagonist naloxone and has been linked to a non μ opioid pathway. The delta selective opioid antagonist, naltrindole, suppresses the antinociceptive effects of midazolam suggesting that intrathecal midazolam is involved in the release of an endogenous opioid acting at spinal delta opioid receptors. These results provide further evidence that there may be a sudeful potentiation of antinociceptive and analgesic effects to be gained by concurrent therapy with a μ selective opioid like fentanyl and midazolam.

Recovery of ambulation and ability to void are important factors determining duration of recovery room stay. Our study quantitatively demonstrates that addition of midazolam does not affect the onset, quality or duration of motor blockade. Neither the recovery of ambulation was delayed; nor did not contribute to an increased duration of recovery form motor blockade.

There was no incidence Hypoxia, Neurological symptoms of nausea vomiting, prutitis hiccoughs or post-dural puncture headache and post operative of pain.

Though all benzodiazepine antagonist produce dose related respiratory depression by decreasing the sensitivity of medullary respiratory centres to hypercapnia, all two groups in our study neither showed any evidence of respiratory depression, nor any significant difference in oxygen saturation between the groups.

The major advantage of the pain relief of spinal benzodiazepines is the absence of motor and sympathetic

blockade and postural hypotension. Thee were no significant differences in haemodynamic changes in both medazolam group II.

In contradiction to experimental findings, most of the patients in the study in the midazolam group showed good sedation. Sedation has been reported with high doses of epidural midazolam (75-100µg/kg) but not in the dose administered intrathecally. He analgesic effect of midazolam stems from its action at the spinal cord, while its sedative and hyperalgesic stems from its action at the spinal cord, while its sedative and hyperalgesic effects are a function of its supraspinal action. The induction of both somnolence and sedation by a high concentration of intrathecal midazolam suggests that at these high concentrations diffusion of significant quantities of the drug occurs into the brain. The sedation can also be due to the systemic absorption of the drug from the CSF. In our study most of the patients in the midazolam group appeared to be sedated after 15 minutes of injecting the study solution and the sedation lasted for 30-45 minutes. Thus at the end of the operation, patients were fully awake responding to verbal commands and recovery was not prolonged. None of the subjects received any sedation intraoperatively.

The most serious risk of intrathecal midazolam is its possible neurotoxicity. So far, animal studies have revealed no damage to the spinal cord, nerve roots or meninges. In vitro studies with changes in transparency and pH of SF by midazolam have suggested that clinically useful doses of intrathecal midazolam are unlikely to be neurotoxic. In our study, we paid special attention to any potential side effects or complications during the perioperative period. There were no neurological complications and good analgesis effect postoperatively.

CONCLUSION

In conclusion, our findings suggest that adding of 1.5 mg midazolam to 1.5 ml of hyperbaric bupivacaine in spinal aneasthesia fo trans urethral resection of prostate surgery

1. Enhance the efficacy of bupivacaine hyperbaric by prolonging the duration of sensory bock without prolonged motor recovery.
2. It also provided sedation intraoperatively
3. There was no significant difference in the haemodyamic changes between all group.
4. No significant side effect were noted in between all three groups.
5. Prolonged analgesic efficacy noted in patients of group II as compare to group I.

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