Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE6, 2024

Original Research Article

To Evaluate and Compare the Efficacy of Intrathecally Administered Midazolam and Fentanyl in Combination with Hyperbaric Bupivacaine.

Dr. C M Raghudhar[1] (Junior Consultant) & Dr. Surbhi Sahay[2] (Professor)

Ragavi Hospital, Hyderabad[1]
Department of Anaesthesia & Critical Care, Bhopal Memorial Hospital & Research Centre, Bhopal[2]

Corresponding Author: Dr. C M Raghudhar

Abstract

Background & Methods: The aim of the study is to evaluate & compare the efficacy of intrathecally administered midazolam & fentanyl in combination with hyperbaric bupivacaine. 186 patients of ASA grade I & II scheduled for elective lower abdominal & urologic surgical procedures were selected for the study & allocated into two groups (group M & F).

Results: The quality of anesthesia was assessed after intrathecal administration of the study drugs with the help of modified bromage scale in midazolam plus bupivacaine (M) group compared to fentanyl plus bupivacaine group (F) group & the difference was not statistically significant ($p > 0.05$).

Conclusion: Intrathecally administered 15 mg of 0.5% hyperbaric bupivacaine & 25mcg (0.5ml) of fentanyl decreases time of onset & increases duration of block and analgesia during intraoperative & early postoperative period in comparison to 15mg of 0.5% hyperbaric bupivacaine & 1mg (0.2ml) of preservative free midazolam & 0.3 ml of 0.9% Sodium chloride solution.

Keywords: efficacy, intrathecally, midazolam, fentanyl, hyperbaric & bupivacaine.
Study Design: Comparative Study.

1. INTRODUCTION

One of the primary aims of anaesthesia is to alleviate the patient's pain & agony, thereby permitting the performance of surgical procedures without any discomfort. Relief of postoperative pain has gained real importance in recent years considering the central, peripheral & immunological stress response to tissue injury. [1]

Spinal Anaesthesia is used extensively for lower abdominal & lower extremity surgeries because it has distinct advantages over general anaesthesia. Lignocaine & bupivacaine are the two most commonly used local anaesthetic agents for spinal anaesthesia. Adjuvants like opioids or ketamine are sometimes combined with local anaesthetic for spinal anaesthesia. The rationale for combining an adjuvant to local anaesthetic drug is to lower the dose of each agent & maintaining analgesic efficacy whilst reducing the incidence & severity of side effects. Spinal local anaesthetics & opioids have synergistic antinociceptive effects & opioids

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE6, 2024

have been shown to decrease the requirement of local anaesthetics & to reduce the incidence of hypotension.[2]

Spinal subarachnoid block is one of the most versatile regional anaesthetic techniques available today. Regional anaesthesia offers several advantages over general anaesthesia blunts stress response to surgery, decreases intraoperative blood loss, lowers the incidence of postoperative thromboembolic events, & provides analgesia in early postoperative period [3].

Opioids like morphine & fentanyl are extensively used as an adjunct to local anaesthetics in neuraxial blockade to enhance the duration of postoperative analgesia [4]. However worrisome adverse effects like pruritus, urinary retention, postoperative vomiting & respiratory depression limit the use of opioids in such procedures.

Midazolam produces a synergistic effect on postoperative analgesia when administered intrathecally with bupivacaine [5]. Previous reports have shown that administration of intrathecal midazolam with local anesthetic prolongs the duration of spinal anaesthesia & produces longer postoperative analgesia after lower abdominal & per anal surgeries [6].

None of these studies reported any serious adverse effects in patients receiving intrathecal midazolam. A large cohort study investigating the adverse neurological effects of intrathecal midazolam has also found no association between intrathecal midazolam & neurologic symptoms [7]. Midazolam, a water-soluble benzodiazepine, produces an analgesic action through the benzodiazepine/aminobutyric acid receptor complex in the spinal cord [8].

Discovery of benzodiazepine receptors in spinal cord in 1977 triggered the use of intrathecal midazolam for prolongation of spinal anaesthesia. In vitro autoradiography has shown that there is a high density of benzodiazepine (GABAA) receptors in Lamina II of the dorsal horn in the human spinal cord, suggesting a possible role in pain modulation [9]. So far different animal studies have revealed no damage to the spinal cord, nerve roots, or meninges & in vitro studies suggested that clinically useful doses of intrathecal midazolam are unlikely to be neurotoxic.

Aims & Objective:

1. To compare the quality and duration of intraoperative anaesthesia and postoperative analgesia among the two groups.
2. To compare the side effects (hypotension and bradycardia) among the two groups.

2. MATERIAL & METHODS

ASA grade I & II patients between 20-65 years of age undergoing lower abdominal and urologic surgeries were included in the study.

Pre anaesthetic checkup was done in the evening before surgery & all patients were kept nil by mouth after midnight. Premedication with ranitidine 150mg & alprazolam 0.25 mg orally on night before surgery & at 6am in the morning of surgery was advised. Patients were explained about the procedure in detail.After shifting the patient to the operating room monitor was attached and base line pulse rate and blood pressure were recorded. Intravenous line was secured with a wide bore canula. Preloading was done with 15- 20ml / kg of crystalloid solution.

After obtaining due approval from Institutional Review Board & Ethical Committee of the hospital , this study was conducted in the Department of Anaesthesia & Critical Care, Bhopal Memorial Hospital & Research Centre over a period of 18 months. Informed consent was taken from all patients prior to study.

Each group had 93 patients and were randomly allocated to receive one of the following drugs:

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE6, 2024

Group M – received 15mg of 0.5% hyperbaric bupivacaine & 1mg (0.2ml) of preservative free midazolam & 0.3 ml of 0.9% Sodium chloride solution.

Group F – received 15 mg of 0.5% hyperbaric bupivacaine & 25mcg (0.5ml) of fentanyl. Total drug volume in all the two groups was 3.5ml in both the groups.

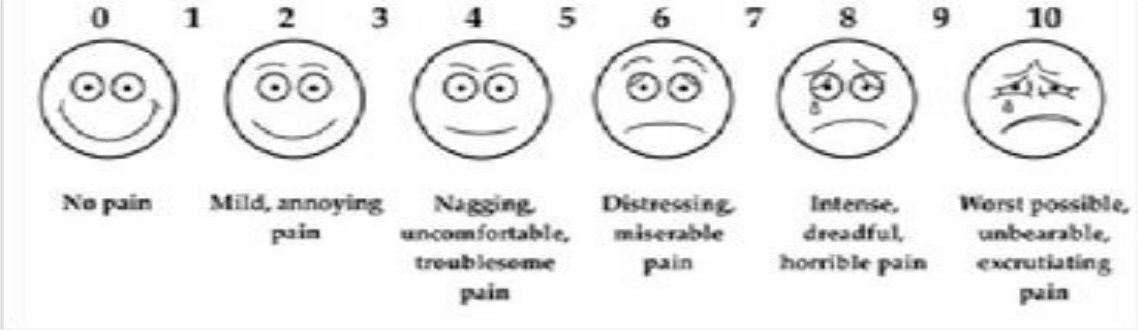
MODIFIED BROMAGE SCALE:
Grade 0 - Full flexion of knees and feet.
Grade 1 - Just able to flex knees, full flexion of feet.
Grade 2 - Unable to flex knees, but some flexion of feet possible.
Grade 3 - Unable to move legs or feet.

The duration of complete analgesia was taken from the time of intrathecal drug administration to the first report of pain. The duration of effective analgesia was taken from the time of intrathecal drug administration to the time of first supplementation with rescue analgesic. Injection diclofenac sodium 1.0 mg / kg intramuscular was the rescue analgesic given if VAS was found to be 4 or more.

ANALGESIA:
Pain in the post operative period was evaluated using Visual analogue scale

Grading of pain	VAS score
Severe pain	8, 9, 10
Moderate pain	4, 5, 6, 7
Mild pain	1, 2, 3
No pain	0

Figure 6: Visual analogue scale



The statistical significance will be brought by student t test.

Justification for sample size

Sample size calculation was done on the basis of total number of elective lower abdominal and urologic surgical procedures out of all other surgeries which were performed in our hospital in last 6 months.

The sample size was calculated according to the following formula.

$$N = \frac{t^2 \times p\,(1-p)}{M^2}$$

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE6, 2024

Description:

N = required sample size.

t = confidence level at 95% (standard value of 1.96).

p = estimated proportion of elective lower abdominal and urologic surgical procedures out of all other surgeries which were performed in our hospital in last 6 months, total 325 cases of elective lower abdominal and urologic surgical procedures were performed out of 2250 total surgeries in last 6 months (p=14%)

M = margin of error at 5% (standard value of 0.05).

Hence required sample size was calculated by using above formula which was 186.

We have included total 186 cases of elective lower abdominal and urologic surgical procedures which fulfilled our inclusion criteria and divided into two groups of 93 each; one is M group and second is F group. After that data collection, analysis and study drugs instillation was done by another anaesthesiologist who was not involved to deliver anaesthesia. So in this way, both patients as well as investigator were unaware about the study drugs.

STATISTICAL ANALYSIS:

The data was analyzed using SPSS 20.0 and all variables were expressed as mean ± standard deviation. The comparison of normally distributed continuous variables between the groups was performed by using unpaired Student t test for comparing the means of both groups and chi-square test was used to find the association between two groups. For all statistical tests, a P value less than 0.05 is considered significant.

3. RESULTS

TABLE -1 MEAN AGE DISTRIBUTION OF THE CASES IN STUDY GROUPS

	Group	N	Mean	Std. Deviation	P value
Age (Years)	MIDAZOLAM + BUPIVACAINE	93	48.7634	8.76430	0.967
	FENTANYL+ BUPIVACAINE	93	48.8172	8.84645	

Mean age of the cases in study groups were almost comparable showing no statistically significant difference (P > 0.05)

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE6, 2024

TABLE 2: TIME OF ONSET IN MINUTES

GROUP	MEAN	SD	
MIDAZOLAM	4.59	1.07	P=0.00016
FENTANYL	4.00	1.12	

We analysed the onsets in minutes after intrathecal injection of drugs in the groups- F & M. Onset of action in minutes was lesser in fentanyl plus bupivacaine (F) group compared to midazolam plus bupivacaine group (M) group & the difference was statistically significant ($p < 0.05$).

TABLE 3: DURATION OF BLOCK IN MINUTES:

GROUP	MEAN	SD	P value
MIDAZOLAM	190	19.20	P=0.00001
FENTANYL	212	22.95	

After study drugs were administered intrathecally, the duration of block(in minutes)was analysed using VAS score and it was lesser in midazolam plus bupivacaine (M) group compared to fentanyl plus bupivacaine group (F) group & the difference was statistically significant ($p < 0.05$).

TABLE 4: DURATION OF ANALGESIA IN MINUTES:

	MEAN	SD	
MIDAZOLAM	**198**	**18.66**	**P=0.00001**
FENTANYL	**223**	**21.17**	

We also analysed the duration of analgesia in minutes after intrathecal injection of drugs in both group F and M with the help of VAS score. Duration of analgesia was less in midazolam plus bupivacaine (M) group compared to fentanyl plus bupivacaine group (F) group and the difference was statistically significant ($p < 0.05$).

TABLE 5: QUALITY OF ANESTHESIA

MODIFIED BROMAGE SCALE			TOTAL
	MIDAZOLAM GROUP	FENTANYL GROUP	
0	**0**	**0**	**0**
1	**0**	**0**	**0**
2	**2**	**0**	**2**
3	**91**	**93**	**184**

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE6, 2024

	MEDIAN	P VALUE
MIDAZOLAM	**3**	**P=0.08**
FENTANYL	**3**	

After the study drugs were administered intrathecally, the quality of anesthesia was analysed with the help of modified bromage scale in midazolam plus bupivacaine (M) group compared to fentanyl plus bupivacaine group (F) group & the difference was not statistically significant ($p > 0.05$).

TABLE 6: INCIDENCES OF HYPOTENSION

	HYPOTENSION	NO HYPOTENSION		
MIDAZOLAM	**19**	**74**	**93**	**P=0.067**
FENTANYL	**30**	**63**	**93**	
TOTAL	**49**	**137**	**186**	

No statistically significant difference was found between the groups regarding side effect hypotension ($P > 0.05$).

4. DISCUSSION

In our study, we compared the onset of intraoperative anaesthesia & early postoperative analgesic effect of intrathecal bupivacaine with midazolam versus bupivacaine with fentanyl in patients undergoing elective lower abdominal & urologic surgical procedures. Our results showed that the addition of fentanyl to bupivacaine decreases time of onset & increases quality & duration of intraoperative anaesthesia.

Bacha et. al., 2015 demonstrated that the use of intrathecal fentanyl as adjuvant to hyperbaric bupivacaine in orthopaedic surgical procedures provides good quality intraoperative analgesia & hemodynamic stability with minimal side effects & excellent quality of postoperative analgesia[10].

Deepak V. Dhummansure (2014) compared the efficacy of sensory & motor block, degree of postoperative analgesia & adverse effects of clonidine & fentanyl used intrathecally with hyperbaric bupivacaine for spinal anaesthesia[11].

E. Freye & A. Mizutani (2013) concluded that addition of preservative free midazolam to 0.5% hyperbaric bupivacaine for subarachnoid block in infraumbilical surgery prolongs the duration of effective analgesia as compared to bupivacaine alone & delays the need for postoperative rescue analgesics without having any sedative effect, pruritis, or respiratory depression. The use of intrathecal midazolam also decreases the incidence of postoperative nausea vomiting (PONV). Intrathecal midazolam does not have any clinically significant effect on perioperative hemodynamics. A small diluted dose (1 to 2.5mg, <1mg/mLconcentration) of preservative-free intrathecal midazolam appears to have few systemic side effects & is free of short-term neurotoxicity[12].

In 2001, Kim & Lee conducted a study to evaluate the postoperative analgesic effect of intrathecal midazolam when co administered with bupivacaine in patients undergoing haemorrhoidectomy. The authors found that the analgesic effect of intrathecal bupivacaine was potentiated by intrathecal midazolam. The addition of 1 or 2 mg of intrathecal midazolam prolonged the postoperative analgesic effect of bupivacaine by approximately 2 h

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE6, 2024

& 4.5 h, respectively, compared with controls after haemorrhoidectomy. In addition, midazolam-treated groups used less analgesic in the first 24 h after surgery. The result suggested a dose-dependent effect of intrathecal midazolam[13].
Vandana Talwar, Anutam Rai, Ritika Gandhi, Anoop Raj Gogia (2008): compared the effect of intrathecal fentanyl with that of intrathecal midazolam in combination with bupivacaine on the duration & quality of spinal blockade[14].

5. CONCLUSION

Intrathecally administered 15 mg of 0.5% hyperbaric bupivacaine & 25mcg (0.5ml) of fentanyl decreases time of onset & increases duration of block and analgesia in intraoperative & early postoperative period in comparison to 15mg of 0.5% hyperbaric bupivacaine & 1mg (0.2ml) of preservative free midazolam & 0.3 ml of 0.9% sodium chloride solution.The difference in quality of anaesthesia was not statistically significant between the two groups.

6. REFERENCE:

1. Jeshnu Prakash Tople, Amol Singam, Satish Gosavi, Aruna Vijay Chandak: Comparison of intrathecal bupivacaine (17.5mg) with preservative free Midazolam (1mg) versus intrathecal Bupivacaine (17.5mg) for postoperative pain relief in lower limb surgeries Dept of Anaesthesia, J.N. Medical College, Wardha DMIMS, India Journal DOI: 10.7439 / ijbar coden: ijbabn. International journal of biomedical & advance research ijbar (2013) 04 (02)
2. ASHOK SHANKAR BHADE MD, MAHESH NAGAPPA MD Ashok Shankar Bhade MD, Professor & HOD Mahesh Nagappa MBBS, MD Senior Resident Department of Anaesthesiology & Critical Care Jawaharlal Institute of Postgraduate Medical Education & Research Pondicherry 605006 India.
3. Anirban Chattopadhyay, Souvik Maitra, Suvadeep Sen, Sulagna Bhattacharjee, Amitava Layek, Sugata Pal, & Kakali Ghosh: A Study to Compare the Analgesic Efficacy of Intrathecal Bupivacaine Alone with Intrathecal Bupivacaine Midazolam Combination in Patients Undergoing Elective Infraumbilical Surgery. Hindawi Publishing Corporation Anesthesiology Research & Practice Volume 2013, Article ID 567134, 5 pages.
4. Yegin A, Sanli S, Hadimioglu N, et al. Intrathecal fentanyl added to hyperbaric ropivacaine for transurethral resection of the prostate. Acta Anaesthesiol Scand. 2005;49 : 401–5.
5. Otokwala JG, Fyneface-Ogan S, Mato CN. Comparative effects of single shot low dose spinal bupivacaine only & bupivacaine with fentanyl on labour outcome. Niger J Med. 2013 ; 22:279–85.
6. Bozdogan Ozyilkan N, Kocum A, Sener M, et al. Comparison of intrathecal levobupivacaine combined with sufentanil, fentanyl, or placebo for elective caesarean section: a prospective, randomized, double-blind, controlled study. Curr Ther Res Clin Exp. 2013;75:64–70.
7. Wong CA, Scavone BM, Slavenas JP, et al. Efficacy & side effect profile of varying doses of intrathecal fentanyl added to bupivacaine for labor analgesia. Int J Obstet Anesth. 2004;13:19–24.
8. Raffaeli W, Marconi G, Fanelli G, et al. Opioid-related side-effects after intrathecal morphine. Eur J Anaesthesiol. 2006; 23: 605–10.

ISSN: 0975-3583, 0976-2833 VOL15, ISSUE6, 2024

9. Nishiyama T, Hanaoka K. Midazolam can potentiate the analgesic effects of intrathecal bupivacaine on thermal- or inflammatoryinduced pain. Anesth Analg. 2003;96:1386–91.
10. M. H. Kim, Y. M. Lee:Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. Br. J. Anaesth. (2001) 86 (1): 77-79.
11. Deepak V. Dhummansure, S. G. Patil, M. M. Haque, Subooh Kamtikar. "A Comparative Study of the Effects of Intrathecal Bupivacaine (0.5%) with Clonidine (1μg/kg) versus Intrathecal Bupivacaine (0.5%) with Fentanyl (25μg) for Spinal Anaesthesia". Journal of Evidence based Medicine and Healthcare; Volume 1, Issue 13, December 01, 2014; Page: 1621-1634.
12. E. Freye & A. Mizutani Midazolam in Subarachnoid Block: Current Evidence ISRN Anesthesiology Volume 2013, Article ID 202835, 7 pages
13. Kim MH, Lee YM. Intrathecal midazolam increases the analgesic effects of spinal blockade with bupivacaine in patients undergoing haemorrhoidectomy. Br J Anaesth. 2001; 86: 77–9.
14. Vandana Talwar, Anutam Rai, Ritika Gandhi, Anoop Raj Gogia: Comparison of Intrathecal Midazolam & Fentanyl Added to Bupivacaine for Lower Limb Surgery J Anaesth Clin Pharmacol 2008; 24(4): 447-450.