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Comparison of Intrathecal Adjuvant Midazolam and Fentanyl with Hyperbaric Bupivacaine for Post-Operative Analgesia in Patient Undergoing Total Abdominal Hysterectomy

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Abstract

Background: Spinal anaesthesia is preferred technique for conducting abdominal hysterectomy, but it is insufficient to provide post-operative analgesia adequately. The addition of local anaesthetic adjuvants increases subarachnoid block efficacy and prolongs postoperative analgesia. Due to its fast onset with a limited time of action with minimal cephalic spread, Fentanyl is preferred as an adjuvant in spinal anaesthesia. Adding Fentanyl to a low dose, Bupivacaine offers improved surgical anaesthesia and increased block reliability. Intrathecal midazolam raises threshold for pain by binding to the Benzodiazepine receptors in spinal cord.

Objectives: To compare theDuration of the postoperative analgesia (Time of 1st rescue Analgesic) between intrathecal administration of Midazolam (2.5mg) and fentanyl (25µg). To compare the duration and onset of sensory and motor block (modified bromage scale) , the effect on haemodynamic parameter, 24hrs analgesic(paracetamol 15-20mg/kg) requirement(No of injection), Degree of sedation and side –effects (post-operative nausea and vomiting,pruritus,shivering ,urinary retention and any other).

Methodology:It is a comparative prospective study which will be conducted on 60 women posted for total abdominal hysterectomy. They will randomly divided into two groups having thirty patients in both groups. Group M will receive 2.5ml of 0.5% hyperbaric bupivacaine with 0.5ml (2.5mg) midazolam preservative free and Group F will receive 2.5ml 0.5% hyperbaric bupivacaine with 0.5ml (25µg) fentanyl intrathecally. The onset of sensory and motor block, duration of block, hemodynamic parameter, sedation score, total postoperative analgesia time and side effects if any will be recorded.
Expected result :We are trying to prove the hypothesis that addition of which adjuvant 2.5gm midazolam or 25 µg fentanyl given intrathecally to hyperbaric bupivacaine prolongs the duration post- operative analgesia more as compared to other.

Discussion: We will try to prove that addition of adjuvant fentanyl 25µg as compared to midazolam 2.5mg with 0.5% hyperbaric bupivacaine 12.5mg prolongs the post-operative analgesia when given intrathecally.

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Keywords: Intrathecal midazolam; fentanyl; hyperbaric bupivacaine; total abdominal hysterectomy.

INTRODUCTION

Spinal anaesthesia, a type of regional anaesthesia where nerve root conduction block is accomplished by injecting a small volume of local anaesthetic solution via a lumbar puncture into the sub-arachnoid space. The preferred technique for infra-umbilical surgery is spinal anaesthesia, which is economical, easy to perform and provides a quick onset of anaesthesia with full muscle relaxation [1]. Bupivacaine is the most popular intrathecal agent, however, it is in insufficient to provide post-operative analgesia even with high sensory block. It also requires high dose of rescue analgesia in post-operative period. It is the moral responsibility of anaesthesiologist to provide a safe and pain free post-operative period to the patient with/by using various combination of drugs or techniques, so that patient can be discharged early and also be able to ambulate freely. Addition of adjuvant to local anaesthetic agent for subarachnoid blockage results into potentiation of blockade effect and prolongation of postoperative analgesia. It is helpful in reducing the usage of post-operative analgesic and dosage of Bupivacaine. It also maintains the cardio-vascular stability.

Fentanyl, one type of phenyl piperidine derivative is a synthetic μ opioid receptor agonist. Due to its high lipophilicity, it is highly potent. In spinal anaesthesia, it is favored as an adjuvant due to its rapid onset with a limited time of operation with minimal cephalic spread. Due to its high lipophilicity, it is highly potent. In spinal anaesthesia, it is favored as an adjuvant due to its rapid onset with a limited time of operation with minimal cephalic spread. Low-dose added fentanyl Bupivacaine offers improved surgical anaesthesia and increased block reliability. However, pruritus, nausea, vomiting, respiratory depression, tremor and urinary retention as side effect for which studies on alternative adjuvant is necessitated.

In the quest of newer, safer, local anaesthetic additive, researchers have found that Benzodiazepines lead to segmental block of nociception without any adverse effect on cardiovascular, respiratory and nervous system. Thereceptors for Benzodiazepine are present in the nervous system and the spinal cord which is linked with the gamma-amino-butyric acid receptors (GABA receptors), intrathecal midazolam increases the threshold for pain by binding to BZD receptors which are present in the spinal cord [2,3].

RESEARCH QUESTION:

Which is more effective in providing post opearative analgesia i.e Midazolam 2.5mg or fentanyl 25μg as an adjuvant to 0.5% hyperbaric bupivacaine ??

RATIONALE

Many studies have been conducted on individual potency of fentanyl and midazolam .In our study we wanted to compare which adjuvant is better with 12.5mg hyperbaric bupivacaine when administered intrathecally.

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AIM

To compare the efficacy between Intrathecal Midazolam 0.5ml(2.5mg) with Fentanyl 0.5 ml (25µg) as adjuvant and 0.5% Hyperbaric Bupivacaine 2.5ml(12.5mg) for Post-Operative Analgesia in Patients Undergoing TAH (Total abdominal hysterectomy).

OBJECTIVES

Primary objective:

To determine the duration of post-operative analgesia between Midazolam with Fentanyl as an adjuvant and 0.5% Hyperbaric Bupivacaine in patients receiving Sub-arachnoid block for TAH (Total abdominal hysterectomy).

Secondary objective:

To compare

i. the duration and onset of sensory and motor block level
ii. two segment regression time
iii. the hemodynamic stability
iv. the number of rescue analgesic in 24 hours between them
v. side effects- Post-operative nausea vomiting, pruritus, shivering, urinary retention, sedation, post spinal headache and any other

MATERIAL AND METHOD

The study will be conducted in Anaesthesiology department, Jawaharlal Nehru Medical College (JNMC), DMIMS, Sawangi (M), Wardha after the approval of IinstitutionalEthics Ccommittee. Written and informed consent will be obtained from all patients in their vernacular language willing to participate in the study prior to procedure.

a) *Study design*

- Study period : 2 years
- Study area: Department of Anaesthesiology JNMC & AVBRH.
- Research design : Comparative Prospective Study
- Study population : female patient 35-75yrs of age

b) *Inclusion criteria*

- Female age between 35-75 yrs
- Total abdominal hysterectomy under subarachnoid block
- Duration of surgery 2hrs
- ASA I &II
- MPC I & II
- Patients giving consent for study

c) *Exclusion criteria*

- Patient refusal to participate in study
- Known allergy to Midazolam, Fentanyl
- ASA > grade III
- Pre-operative hepatic or renal dysfunction
- All common contraindications for spinal anaesthesia like increased intracranial pressure, spine deformity.

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- Serious cardiac or respiratory disease,
- High abnormal prothrombin time(PT) or activated partialthromboplastin time (aPTT)
- Congenital or acquired coagulopathy
- History of thromboembolic disease
- Local site infection
- Patients with neurological and musculoskeletal disease

d) *Sampling size & technique*

After the approval from the institutional ethics committee, the study will be conducted on 60 patient undergoing after fulfilling all inclusion and exclusion criteria.

- Group M (n=20) Injection Bupivacaine 0.5% (heavy) 2.5ml (12.5mg) + Injection Midazolam 0.5ml (2.5mg) preservative free . (reference from Parmar and Shah)
- Group F (n=20) Injection Bupivacaine 0.5% (heavy) 2.5ml (12.5mg) + Injection Fentanyl 0.5ml (25 µg) preservative free. (Reference from Parmar and Shah)

$$n = 2 \times \frac{(SD)^2 \left(Z_{\alpha/2} + Z_{\beta} \right)^2}{d^2}$$

Where, n = sample size

SD= standard deviation found in previous study was found to be 9.23

D= difference between mean values, In our study, we expect it to be 7.2

$Z_{\alpha/2} = Z_{0.05/2} = Z_{0.025} = 1.96$ (with an error of 5%)

$Z_{\beta} = Z_{0.20} = 0.842$ (at 80 power)

So,

$$n = 2 \times \frac{(9.23)^2 (1.96 + 0.84)^2}{(7.2)^2}$$

$= 25.8$

So, we have taken 30 patients in each group considering dropout.

METHODOLOGY

Pre-operative assessment

i. All patients will undergo a pre-anaesthetic check-up a day before the procedure.

ii. Basic patient details, history and presenting complaints of the illness, general and systemic examination and basic blood and lab investigations will be noted.

iii. Patients will be explained about the study purpose, its merits and demerits. Informed written consent will be obtained from each patient that will be included in the study.

iv. They will be asked to maintain a fasting status for a minimum of 8 hours prior to the surgery.

v. The patients for the study will be distributed randomlyinto 2 groups.

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Group M	Group M (n=30) Injection Bupivacaine 0.5% (heavy) 2.5ml (12.5mg) + Injection Midazolam 0.5ml (2.5mg)	Total Volume= 3ml
Group F	Group F (n=30) Injection Bupivacaine 0.5% (heavy) 2.5ml (12.5mg) + Injection Fentanyl 0.5ml (25 µg)	Total Volume= 3ml

f) *Intra- operative*

i. On the arrival of the patient in the operating room, pulse oximeter, NIBP monitor and ECG will be attached.

ii. IV line will be secured with 18g Intra-cath and Ringer Lactate will be started with 10-15ml/Kg.

iii. Baseline vitals Heart rate (HR), respiratory rate (RR) ,systolic blood pressure (SBP) ,Spo2 will be recorded and a continuous visual display of electrocardiogram from lead II.

iv. All patients will be given premedication Inj. Ondansetron 75-100 mcg/kg IV 10 minutes prior to anaesthesia procedure.

v. Subarachnoid block will be performed through midline approach with 25 gauge with patient in left lateral/ sitting position, under all aseptic precautions.

Quinke's spinal needle in intervertebral space L3-4/L4-5.

Group M	Group M (n=30) Injection Bupivacaine 0.5% (heavy) 2.5ml (12.5mg) + Injection Midazolam 0.5ml (2.5mg)	Total Volume= 3ml
Group F	Group F (n=30) Injection Bupivacaine 0.5% (heavy) 2.5ml (12.5mg) + Injection Fentanyl 0.5ml (25 µg)	Total Volume= 3ml

After completion of procedure, patient will be turned immediately to supine position. All patients will receive supplementation of oxygen (4 litres per minute by Hudson mask).

vi. The following parameters will be recorded.

1. Onset of the sensory and the motor blockade
2. Maximum level of sensory blockade which is attained and the time taken for the sensory blockade will be noted.
3. Two segment regression time of sensory blockade
4. Level of sedation
5. Assessment of postoperative pain by VAS
6. Time to first rescue analgesia
7. Adverse effects if any.

Testing for sensory blockade will be done using pin prick method with a blunt tipped needle after every 2 mins until surgical anaesthesia achieved at the dermatome level T10. Modified Bromage scale will be used to assess the quality of motor blockade [4].

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DEFINITIONS

- Onset of sensory block is termed as time taken from the completion of injection of study drug till the patient doesn't feel pinprick at the level of T10.
- The time taken to achieve the maximum sensory blockade is defined as the time taken from end of study drug injection to the maximum sensory blockade achieved
- Onset of motor blockade. Is the time interval from administration of study drug to the achievement of bromage score 1.
- Duration of 2 segment sensory regression is known as the time taken by two segments from the maximum degree of sensory blockade reached until the sensation has regressed.
- Level of sedation assessed by Ramsay Scale.
- The quality analgesia will be assessed by analyzing the degree of pain using the Visual Analog Scale (VAS)
- Duration of analgesia is defined as the time taken from onset of sensory block at the highest dermatome to the time taken for the patient to experience pain sensation at surgical site.
- Hemodynamic parameters shall be monitored every two minutes for the first ten minutes, every five minutes for the next half an hour and every fifteen minutes thereafter till the end of the surgery.
- Patients will receive Inj. Glycopyrolate 0.2 mg when the heart rate (HR) falls below 20% of baseline (bradycardia) and Inj. Mephentermine in titrated boluses when there is hypotension (fall in blood pressure below 20% of baseline). Any side-effects seen after administration of study drug will be noted and treated appropriately. IV fluids will be given in accordance to the patient's weight and as per intraoperative fluid loss during surgery.
- During the surgical procedure, adverse effects like anxiety, nausea,pruritus, vomiting and shivering will be recorded. Anxiety can be treated with sedation using 1mg of Injection Midazolam i/v.
- Nausea and vomiting will be treated with 4mg Ondensetroni/v, shivering with injection Tramadol 50mg i/v and pruritus or any allergic reactions managed with Inj Hydrocortisone 100mg and injection Pheniramine Maleate.

After the surgery the patients will be shifted to the postoperative ward. There they will be monitored every 30 minutes for the first 6 hours and thereafter every 24 hours. When the patient will have a VAS score of more than or equal to 4, rescue analgesia will be given with iv paracetamol (15-20mg/kg)

Degree of motor block-using the Modified Bromage Motor function scale

Grade	Criteria	Degree of block
I	Free movement of legs and feet	Nil (0%)
II	Just able to flex knees with free movement of feet	Partial (33%)
III	Unable to flex knees, but with free movement of feet	Almost complete (66%)
IV	Unable to move legs or feet	Complete (100%)

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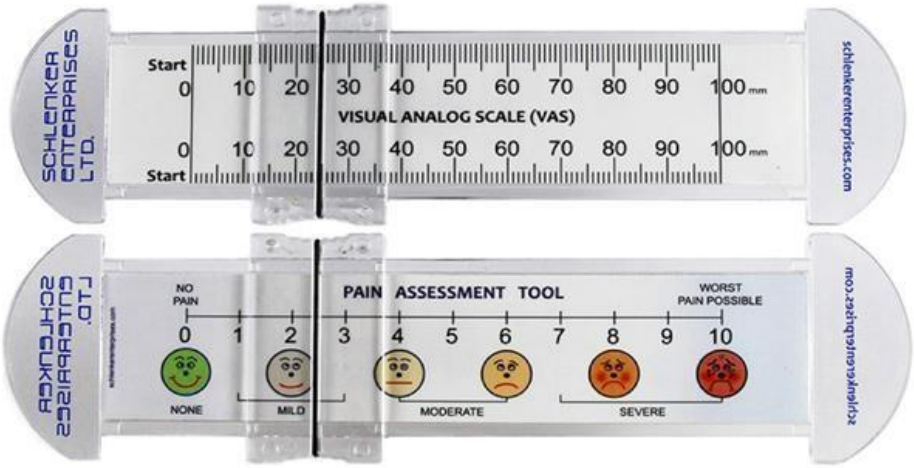
Quality of analgesia: Using the VAS Score



Sedation scale using the modified Ramsey Sedation Scale [5]

0	Paralysed, unable to evaluate
1	Awake
2	Lightly sedated
3	Mod sedated, follows simple commands
4	Deeply sedated, responds to non-painful stimuli
5	Deeply sedated, responds to painful stimuli
6	Deeply sedated, unresponsive to non-painful stimuli

EXPECTED RESULT:

In our study we expect sensory regression to S2 to be prolonged in the Group F as compared toGroup M. However, the duration of motor blockade is comparable between Group M and Group F. Quality of intraoperative anesthesia is expected better in Group F. We also expect duration of complete and effective analgesia is more in Group F as compared to Group M. Quality of Vas will be better in Group F than Group M.

DISCUSSION:

In our study we will demonstrate that addition of Fentanyl (25µ) to 0.5 % hyperbaric bupivacaine (12.5mg) intrathecally in patientsundergoing total abdominal hysterectomy improves better quality of anesthesia and post-operative analgesia with hemodynamic stability and minimal side effects as compared to addition of intrathecal midazolam (2.5mg) to 0.5 % hyperbaric bupivacaine (12.5mg) for patients undergoing total abdominal hysterectomy.

Yekdas (2019) reported that Fentanyl has longer time to fast pain than Midazolam and the most common side effect seen in Fentanyl group is pruritus, tremor, urinary retention and post-spinal headache. But in case of Midazolam, hypotension is significantly higher than the other groups [6]. So it may be suggested that intrathecal Midazolam can be used as an

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adjuvant in case of pregnancy induced hypertensive patient undergoing an elective caesarean section [3, 7]. The most extreme risk of intrathecal midazolam is its possible neurotoxicity. Animal tests have shown no damage to the nerve roots, spinal cord or meningitis to date [8, 9]. Some studies have been published on the spinal application of midazolam in humans. No clinical neurological deficits were caused by a single intrathecal injection of 2 mg midazolam and patients with chronic low back pain developed substantial analgesia for 2 months. [9, 10].No side effects was noticed with Intrathecal midazolam following leg surgery. [9, 11]. Somatic pain is an antinociceptive effect against visceral pain. In addition to the efficacy of intrathecal midazolam against somatic pain has been seen in rabbits who have undergone intestinal distension and in humans who have undergone caesarean section [12]. In 4 patients with refractory neurogenic and musculoskeletal pain, intrathecal midazolam with doses of ≤6 mg day^{-1} is being used in a continuous infusion for a long period of time. In vitro tests have indicated that intrathecal midazolam in clinically useful doses are unlikely to be neurotoxic [13, 14]. Careful attention is needed during the perioperative period to any possible side effects or complications. Neurological problems were not present. Intrathecal midazolam had a segmental analgesic influence. It has no alteration in reflexes or sympathetic tone [9, 14].

Routray et al. (2017) suggested that Fentanyl in addition to Bupivacaine in spinal anaesthesia may be a suitable choice when sedation is not desirable [15]. Research reports also indicated that Fentanyl and Midazolam improves the duration and onset of motor and sensory block with relatively haemodynamic stability, increases duration of analgesia and decreases consumption of systemic analgesics in comparison to Bupivacaine alone [16, 17]. This findings are in good agreement with Sawhney et al. (2019) [18]. They studied on a double-blind randomised controlled trial using Midazolam and Fentanyl as an adjunct. The authors found that Fentanyl performs better than Midazolam in lower limb surgery. They also noted that most patients received at least one dose of rescue analgesic; however those receiving fentanyl reported better postoperative analgesia than those in the midazolam [18].

Parmar and Shah demonstrated that when Fentanyl (25µg) and Midazolam (2.5mg) with low dose Bupivacaine (7.5mg) intrathecally taken in undergoing caesarean section, it improves the quality of anaesthesia with minimal side effect without compromising neo-natal outcome [19]. But Vincenzi et al. (2020) suggested that combination of Midazolam and ketamine is preferable to only Fentanyl for elderly people (>75 years). They observed that thoracic continuous spinal anaesthesia with local anaesthetic plus midazolam and ketamine was superior to local anaesthetic plus fentanyl. It resulted in reducing in incidence of respiratory depression, lowering the intraoperative sedating medications and time to first flatus [20].Bhuyanet. al conducted a study on analgesic efficacy of intrathecal bupivacaine and fentanyl with intrathecal midazolam for lower limb surgeries [21]. Similar studies were reported by Singh and Sen [22], Dongreet. al [23] and Rajan et. al [24]. Few of the related studies were reviewed [25-29].

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