A Comparative Prospective Study Between Intrathecal Midazolam & Nalbuphine as an adjuvant with Hyperbaric Bupivacaine for Post-Operative Analgesia in Total Abdominal Hysterectomy.

ABSTRACT

Background: Subarachnoid block is the preferred form of regional anaesthesia for obstetric surgeries. In it local anesthetic agents alone are insufficient in providing adequate post-operative analgesia, which is an important factor for the patients & ~~is~~ the sole essence of anaesthesia. Adding adjuvant will result in better quality, efficacy of SAB & will prolong analgesia postoperatively. Due to minimal hemodynamic & respiratory complications Nalbuphine, an opioid can be favored as ~~an adjuvants~~an adjuvant to subarachnoid block. Addition of Nalbuphine in limiting doses to Hyperbaric Bupivacaine offers improved block quality & adequate pre & post-operative analgesia. Midazolam, a ~~imidazobenzodiazepine given~~imidazobenzodiazepine given intrathecally raises the threshold of pain, ~~it also~~ has hypnotic, anticonvulsant, muscle relaxant & amnesic effects of other benzodiazepines.

Objectives: Primarily to compare the duration of pain relief in postoperative period between administration of Intrathecal Nalbuphine (1mg) & Midazolam(2.5mg) (Timing of 1st rescue analgesic).Secondarily to compare onset of action & duration of motor & sensory block (Modified Bromage Scale), Effect on Hemodynamic Parameters, 24 hours requirement of analgesic(No.of Injection Paracetamol 15-20mg/kg), Degree of sedation(Modified Ramsay Sedation Scale) & After-effects(PONV, Pruritis, Shivering & Retention of urine).

Methodology: Study type conducted will be Comparative Prospective Study on 60 ASA 1 & 2 females in age group 35-75 years, planned for total abdominal hysterectomy will be separated in two equivalent Group M (n=30) & Group N (n=30). Group M will receive combination Midazolam preservative free 0.5 ml (2.5 mg) with 0.5% Hyperbaric Bupivacain 2.5 ml(12.5 mg), & Group N will receive combination Nalbuphine 1 ml (1 mg) with Hyperbaric Bupivacaine (0.5%) 2.5 ml (12.5mg) by Intrathecal Route. Analgesia duration in post-operative period, onset of action & duration of motor & sensory block, effect on hemodynamic parameters, 24hours analgesics requirement, degree of sedation, after-effects if any will be studied & compared.

Conclusion: Expected to prove the hypothesis that adding which of the following adjuvant 1mg Nalbuphine or 2.5mg Midazolam with 0.5% Hyperbaric Bupivacaine intrathecally given in SAB prolongs the postoperative analgesia duration more as compared to other

KEYWORDS: Subarachnoid block, Total Abdominal Hysterectomy, Intrathecal, nalbuphine , Post-Operative Analgesia, midazolam.

Comment [U1]: This should be written in full since some readers may not have the opportunity to read the full manuscript

Comment [U2]: This should be written in full- Post Operative Nausea and Vomiting

INTRODUCTION:

Subarachnoid block was introduced about hundred years ago, & is still the most popular type of regional anaesthesia approach. But, the local anaesthetic drugs (whether isobaric or hyperbaric) used for subarachnoid block do not prolong postoperative pain relief. Anaesthesiologists face this struggle as they oversee peri & post-operative pain ~~control.[~~control. [1] Excessively soaring regional blocks & toxicity due to local anaesthetics are the most common reasons of deaths linked to regional blocks; therefore, decreasing dosage of local anaesthetics, adding adjuvants, usage of latest methodology to circumvent inordinate blocks, & superior tackling of local anaesthetic toxicity are the novel targets for reducing death rate linked to regional anaesthesia.[2]

Subarachnoid block is a preferred technique of anaesthesia as it is easy to carry out, outset of action is rapid, better relaxation of muscle & effectual. ~~Additionally~~Additionally, reduced recovery time, quick return of patient's normal oral intake & safety are its added advantages. Analgesia in postoperative phase is essential to provide comfort & reinstatement of functions effectively, it is one of the main concern of all patients[3,4] Though subarachnoid block is relatively safe its duration of action is short. To overcome this snag various adjuvants are being added per usual. Subarachnoid block with Hyperbaric Bupivacaine 0.5 Percent, along with adjuvants, is consistently administered for surgeries of lower abdomen.[5] Numerous drugs were recognized to be used as adjuvants such as Opioids, Adrenaline, Neostigmine, Midazolam, Ketamine, α-2 agonists (Clonidine, Dexmeditomidine) for lengthening of local anaesthetic analgesia & action in postoperative phase [6,7] ,but drugs have constraints & their own adverse effects.[6]

Nalbuphine, an opioid, has mixed kappa-agonist & mu-antagonist properties. It acts by competitive displacement of other mu-agonists from the receptor site (mu-antagonism). Also, its binding to kappa-receptors produces an agonist effect. Due to this mixed pattern of agonism & antagonism, **Nalbuphine** is a mixed kappa-agonist-mu-antagonist. It has minimal respiratory depression, in contrast to other opioids analgesics acting centrally, because it has mixed partial k-receptor agonist &μ-receptor antagonist activity. [8,9]

Midazolam is a water soluble imidazobenzodiazepine derivative. Midazolam is similar to other benzodiazepines in binding extensively to plasma proteins. Midazolam has hypnotic,anticonvulsant,muscle relaxation & amnesic effects of other benzodiazepines[10,11]

RESEARCH QUESTION

Which is more effective between~~among~~ Midazolam 2.5 mg & Nalbuphine 1 mg when used as an Intrathecal Adjuvant to Hyperbaric Bupivacaine in providing analgesia in post-operative phase?

RATIONALE

Numerous studies have been conducted about individual strength of both the drugs. We want to compare which adjuvant is better when administered intrathecally along with Hyperbaric Bupivacaine {0.5%} 2.5 ml (12.5mg). Hence the motive of the study.

AIM

The aim of the study is to compare the Efficacy of midazolam & nalbuphine when they are added as an Adjuvant with Hyperbaric Bupivacaine {0.5%} intrathecally in patients planned for Total Abdominal Hysterectomy.

OBJECTIVES

Primary :

To compare post-operative analgesia duration between midazolam (2.5 mg) & nalbuphine (1 mg) dose intrathecally given along with 0.5% hyperbaric bupivacaine.

Secondary:

Comparison~~ation~~ of 1) The onset of action & duration of motor & sensory block.

2) The effect on hemodynamic parameters.

3) 24 hour requirement of ~~analgesic(~~analgesic (Paracetamol 15-20 mg/kg)

4) Degree of sedation.

5) After-effects(PONV, pruritus, shivering, retention of urine & Any Other)

MATERIAL & METHODS

STUDY DESIGN

1. Study Period: 2 year (2020-2022)

2. Study Area: Department of Anaesthesiology JNMC & AVBRH.

3. Research Design: Comparative Prospective Study

4. Study Population: Female Patients 35-75 years of age

Comment [U3]: This needs to change since it is a prospective study and 2021 is ending

INCLUSION CRITERIA

- Women in the 35-75 age range.
- TAH under spinal anaesthesia.
- Surgical duration 2 hours
- American society of anaesthesiologist grade 1 & 2
- Mallampati classification 1 & 2

EXCLUSION CRITERIA

- Patient not willing to participate in the study
- American society of anaesthesiologist grade 3 & 4
- SAB injection site infection.
- Patients with Neuromuscular disorders.
- Patients with bleeding diasthesis or on anticoagulant therapy
- Patient allergic to local anaesthetic, midazolam & nalbuphine

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SAMPLING SIZE & TECHNIQUE

After approval of Ethics Committee of the Institution, Comparative & Prospective study will be done on Sixty patients fulfilling all the Inclusion Criteria.

Patients for the study will be randomly allocated into 2 groups:

- Group M (n=30): Midazolam with Bupivacaine
- Group N(n=30): Nalbuphine with Bupivacaine

Sample Size formulae used are as follows:

$$n = \frac{(Z\alpha + Z\beta)^2 [\sigma_1^2 + \sigma_2^2/k]}{\Delta^2}$$

where,

- Zα-level of significance at 5% (95% Confidence Interval) = 1.96
- Zβ -Power of Test = 80% = 0.84

- σ_1 = for Group N, the SD of sensory blockade onset (1.05)
- σ_2 = for Group M, the SD of sensory blockade onset (0.44)
- $\Delta = 3.04 - 1.95 = 0.61$ & $k = 1$

$$n = \frac{(1.96+0.84)^2 [1.05^2 + 0.44^2/1]}{0.61^2}$$

= 27.30

n = 30 patients needed in each group considering dropouts

Refer-determination of size of sample by VK Chandra, NTI Bulletin, 2006, 42/3 & 4, 55-62.

METHODOLOGY

a) Pre-Operative Assessment

1. Patients will be examined for pre-operative assessment a day prior to surgery for final fitness.
2. Patient details, history of presenting illness, airway assessment, spine examination, nutritional status, detailed general& systemic examination, preoperative blood & other lab investigations of the patient will be noted.
3. Patients will be kept NBM Overnight & pre-medicated using. 150 mg of ranitidine, 0.5mg of alprazolam on the eve of surgery.
4. Women fulfilling the inclusion criteria will be informed & explained about the type and motive of the study & consent will be taken in writing..
5. Patients will be randomly separated into 2 Groups- group M, group N by Slips in the Box Method. Patient & the Anaesthesiologist (the outcome's assessor) who will record the perioperative data, will be blinded to the study drug (Double Blind Study).

Table 1. List of Drugs

GROUP	*DRUG GIVEN*	*TOTAL VOLUME*
M	Bupivacaine (H) 2.5ml (12.5mg) of 0.5% + Midazolam 0.5ml (2.5mg)	3ml
N	Bupivacaine (H) 2.5ml (12.5mg) of 0.5% + Nalbuphine 0.1ml (1mg) normal saline 0.9 ml	3ml

b) INTRA-OPERATIVE

1. Upon reaching OT, multi-para monitors will be connected e.g nibp monitor, electrocardiogram & Spo2 monitor. Baseline values will be recorded
2. An i.v access will be established with 18 gauge IV cannula. 10ml/kg of RL will be used to preload.
3. premedication with injection ondansetron 75-100 µ/kg iv shall be done 10 minutes prior to the SAB procedure.
4. SAB will be performed at intervertebral space L3-L4 with 25G Quincke needle using the median approach in the left lateral or sitting position following all aseptic measures. Drug will be injected after clear, free flowing cerebrospinal fluid (CSF) is observed.

Following the procedure patient shall be quickly shifted to supine position.
Supplemental oxygen will be given using Hudson's mask at 4 L/min.

5. Parameters to be recorded are:
i) onset of sensorimotor block
ii) time taken & max. level of sensory block attained .
iii) two segment regression time of Sensory Block.
iv) sedation level
v) postop assessment of pain by VAS.
vi) timing for 1st rescue analgesia.
vii) any harmful effects.

A unsharp tipped needle shall be used to check sensory block (pinprick technique) every 2 minutes till level of surgical anaesthesia is attained at T10 dermatome.[4] Assessment of quality of motor block shall be done using modified bromage scale.

c) BLOCK EVALUATION

SENSORY BLOCK

1) Sensory Blockade will be assessed by Pin Prick Technique using unsharp tipped needle, on mid-clavicular line, every min till block at T6 dermatome is attained
2) After that, Sensory Block will be examined for every 2 minutes till Maximum Sensory Blockade is achieved.

Table 2. GRADES OF SENSORY BLOCKADE

Grade 0	**SHARP PAIN**
Grade 1	**ANALGESIA, DULL SENSATIONS**
Grade 2	**ANESTHESIA, NO SENSATIONS**

SENSORY BLOCK-ONSET & DURATION

- Onset - it is the period between the injection of anaesthesia and sensory block at T10 dermatome.
- Duration - ~~(assessed~~(assessed by two segment regession) - it is the period between injection of anaesthesia and decrease of level of maximum sensory block by two segments.

MOTOR BLOCK

Assessment of the quality of motor block will be carried out using modified bromage scale.

Table 3. List of motor block

0	No Motor Blockade
1	Inability to raise extended leg; able to move knees & feet
2	Inability to raise extended leg & move knees; able to move feet
3	Complete motor block of the limb

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- Monitoring of hemodynamic parameters – every 2 mins for initial 10 mins, every 5 mins for next 30 mins & finally every 15 mins until the surgery is completed.
- If heart rate reduces to 20 percent below baseline, injection glycopyrolate will be administered & if the blood pressure falls 20 percent below the base line, injection

mephentermine will be administered. Side-effects observed following injection of the drug under study shall be recorded and managed.

- I.v fluids will be given keeping in mind the weight of the patient & fluid loss intraoperatively.
- Intraoperatively, side-effects e.g nausea, vomiting, pruritis & shivering will be noted. Inj. ondansetron 4 mg i.v to treat nausea & vomiting, injection tramadol 50 mg i.v for shivering, & injection hydrocort 100 mg i.v & injection pheniramine 25 mg i.v for allergic reactions & pruritus.
- Patient will be shifted to the postoperative ward after surgery is completed. Monitoring, every half an hour for initial six hrs, will be done. Later daily monitoring will be done. ~~If the~~If the patient shows VAS score of 4 or more injection paracetamol 15-20 mg/kg i.v shall be administered as rescue analgesia.

Comment [U5]: This and other abbreviations should be written in full

VISUAL ANALOG SCALE

- VAS will be described to the patient preoperatively.

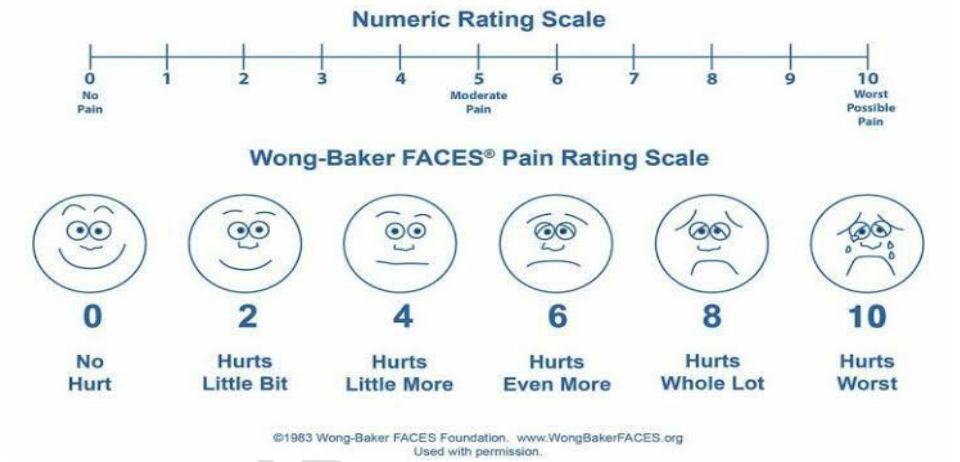

Fig. 1. Numeric rating scale

Table 4. VAS Numeric Pain Distress Scale

SCORE	PAIN
0-2	Absent
2-4	Mild
4-6	Moderate
6-8	Severe
8-10	Unbearable

Table 5. MODIFIED RAMSEY SEDATION SCORE

Sedation Scale	Clinical Response
0	Paralysed, Unable to evaluate
1	Awake
2	Lightly sedated
3	Moderately sedated, follows simple commands
4	Deeply sedated, responds to non-painful stimuli
5	Deeply sedated, responds only to painful stimuli
6	Deeply sedated, unresponsive to painful stimuli

Table 4. Modified Ramsay Sedation Scale

DISCUSSION:

We aim to reveal that addition of intrathecal Nalbuphine 0.1ml(1mg) to 0.5% Bupivacaine 2.5 ml (12.5mg) improves the standard of blockade and postop pain relief, improves haemodynamic stability & minimizes side effects in ~~comparation~~comparison to addition of intrathecal midazolam 0.5ml (2.5mg)to 2.5 ml(12.5mg) of Hyperbaric(0.5%) Bupivacaine in cases of Total Abdominal Hysterectomy.

Fareed Ahmed, et al 2016[12] deduced from their study that combining intrathecal bupivacaine & nalbuphine in cases of abdominal hysterectomy led to improvement of postoperative analgesia, in contrast to the control group. From the 3 doses of nalbuphine that was ~~studied 1~~studied 1.6mg of nalbuphine gave the best results.

T. Das et al in 2017[13] in their study for the relation between intrathecal nalbuphine and postoperative analgesia found out that addition of intrathecal nalbuphine leads to faster onset of sensorimotor block and slow regression of the block. Conversely, Tiwari et al in 2013[14] found out that adding intrathecal nalbuphine does not lead to any change in the onset of sensorimotor blockade. These results were ascribed to the reduced dosing then in the study(0.2mg & 0.4mg) nalbuphine were used. Bharti et al in 2003[15] in their study found out that midazolam increases the duration of motor blockade. Manisha Sapate et al in 2013[16] conduted a double blinded, randomized control trial to find out the results of addition of nalbuphine in abdominal surgeries under spinal anaesthesia (Bupivacaine). It was inferred that addition of nalbuphine improves the standard of block in contrast to views of bupivacaine alone. Further nalbuphine also extends postop pain relief in elderly patients. Several other studies were assessed [17-23].

LIMITATIONS

1 Drug given only by Intrathecal Route

2 This study will be limited to female patients undergoing total abdominal hysterectomy.

3 There is variation in pain threshold in between patients .

CONCLUSION

Adjuvant, Intrathecal Nalbuphine(1 mg), added to Hyperbaric Bupivacaine(12.5 mg) is expected to enhance the quality of block in comparation to (2.5 mg) Midazolam as an adjuvant to Bupivacaine. It is also expected for nalbuphine to provide 8-9 hours long postop

analgesia when utilised in addition to bupivacaine, without producing noteworthy side effects in patients undergoing TAH under sub-arachnoid block.

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