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Original Research Article

Transdermal Nitroglycerine as a Co Adjuvant to Intrathecal Nalbuphine With 0.5% Hyperbaric Bupivacaine for Various Infraumbilical Surgeries

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Abstract:

Purpose: Spinal anesthesia for infraumbilical surgery is common. Various adjuvants are taken to improve sensorimotor characteristics of intrathecal bupivacaine. We have used Nalbuphine as intrathecal adjuvant in both groups & Transdermal NTG in one group as coadjuvant.

Study type: Randomised double blind comparative observational study.

Methods: We have selected 60 adult patients for the study, 30 in each group. Group A: patients received 3 mL of 0.5% heavy bupivacaine 15 mg + 0.1 mL of 1 mg of preservative free nalbuphine (total volume of 3.1mL) and placebo patch was applied after 20 minutes of spinal anesthesia. Group B: patients received 3 mL of 0.5% heavy bupivacaine 15 mg + 0.1 mL of 1 mg of preservative free nalbuphine (total volume of 3.1mL) and tNTG patch of 5 mg was applied after 20 minutes of spinal anesthesia. Demographical data were comparable among the two groups. Statistical analysis was done by noting parameters in MS EXCEL spread sheet in the form of mean ± SD. 'p'<0.05was taken as significant and 'p' value of <0.001 was taken as highly significant.

Results: There was no stastically significant change in vital parameters in both groups. ($p > 0.05$) The sensory &motor characteristics were comparable in the two groups. ($p > 0.05$) Time of 1st rescue analgesia (min) in group A is 327.83 ± 31.61 min and group B is 501.03 ± 40.22 min. ($p < 0.001$). Total analgesic request in 24 hrs in group A is 2.83±0.69 min, group B is 1.83 ± 0.74 which is highly significant stastically. ($p < 0.05$) Complications like shivering, pruritus, nausea and vomiting were more in patients of group A as compared to group B.

Conclusion: Transdermal NTG is good coadjuvant to intrathecal bupivacaine + Nalbuphine for infraumbilical surgery.

Keywords: Infraumbilical surgery, Intrathecal Nalbuphine, Transdermal NTG.

Introduction

In recent years, the use of intrathecal adjuvants has gained popularity, with the intention of reducing the dose of local anesthetics, maintaining hemodynamic stability, delaying the onset of pain in the postoperative period, and thus reducing the demand for postoperative analgesics. Addition of adjuvants ensures faster recovery and reduced hospital stay.

Most commonly used adjuvant in central neuraxial blocks are opioids, however, their adverse effects such as respiratory depression, nausea and vomiting, constipation, and pruritus have prompted further research to develop non opioid adjuvants with less worrisome side effects. Intrathecal (IT) nalbuphine produces a dose dependent anti-nociception when used alone or in combination with local anesthetics. Transdermal NTG patch also provide analgesia.

Nalbuphine is an opioid drug classified as agonist antagonist, with mixed μ antagonist and k agonist properties that provide good intraoperative analgesia and prolonged postoperative analgesia with reduced incidence and severity of μ agonist side effects such as pruritus, nausea, vomiting, urinary retention and respiratory depression.1 Thus it may become an alternative to other centrally

acting opioids such as morphine and fentanyl [l]. Transdermal nitroglycerine has been found to be useful in augmenting the post-operative analgesic effect of intrathecal fentanyl, sufentanyl, clonidine and neostigmine by release of nitric oxide (NO), which increases the intra cellular concentration of cyclic guanosine monophosphate (cGMP). cGMP produces the pain modulation in the central and peripheral nervous system. [2] The primary objective of this study is to assess duration of analgesia& sensorimotor characteristics produced by intrathecal nalbuphine with or without NTG patch when used as adjuvant for spinal anesthesia with hyperbaric bupivacaine.

The Secondary objective is adverse effects observe& haemodynamic changes in each group.

Material and Methods

In the present Randomised comparative study, after taking informed consent & approval from IRB dated 10th April 2018, we have enrolled 60 adult patients of various Infraumbiical (lower abdominal & lower limb) surgeries in our study.

Inclusion criteria:

- ASA I & II of age between 20 and 65 years, presenting for Infraumbiical(lower abdominal& lower limb) surgery under spinal anesthesia from gynecology and general surgery at a tertiary health care center.
- Request for analgesia

Exclusion criteria:

- Patients with psychiatric disorders, chronic pain or any condition that precludes spinal anesthesia
- Patients with coagulopathy, known allergy to the local anesthetic, local site skin infection

Pre-operative evaluation was carried with detailed history, general physical examination. Vital parameters were noted (Pulse, BP, RR, SPO_2) and systemic examination was performed. Each patient was explained in detail regarding the procedure of anesthesia and was explained 0-10 point Linear Visual Analogue Scale (LVAS) on a sheet of paper where score of 0 labelled as no pain and 10 as worst possible pain. An informed valid written consent was obtained from each patient.

Preoperative preparation: All patients were fasted overnight. Vital signs were noted in the pre-operative room and considered as baseline values. In operation theatre anesthesia machine was checked and emergency drugs were kept ready. On entering the OT, non-invasive monitoring was initiated including pulse oximeter, ECG and NIBP. A peripheral venous access was secured on non-dominant hand with 18-gauge cannula and preloading with lactated Ringer's solution was initiated at the rate of 8-10 ml/kg 15 min prior to subarachnoid block. (SAB)

Study groups: Patients were randomly divided into 2 groups with 30 patients in each according to the drugs they received. Randomisation was done by odd & even numbers in sealed opaque envelope.

All patients were given 3ml intrathecal 0.5%heavy bupivacaine 15mg + 0.1ml of 1 mg of preservative free nalbuphine to a total volume of 3.1ml.

0.1 ml of nalbuphine was taken by 4;kappa of Insulin syringe. 1 ml of Nalbuphine 10 mg in 40 kappa of syringe, from that 4 kappa drug was taken to take 1 mg of Nalbuphine. tNTG patch was of 5 mg (total 25 mg and delivers NTG at 20-25 mcg/cm2/hour.)

Placebo/ tNTG patch applied after 20 mins of spinal anaesthesia so spinal bupivacaine get fixed and we can access effect of coadjuvant pacebo/ tNTG patch.

Group A: The placebo patch was applied 20 minutes after spinal anesthesia.

Group B: tNTG patch application after 20 min of spinal anesthesia. All patches in each group were applied on dry clean non hairy non anesthetized area.

All the patients were explained the procedure and it was kept uniform in all patients. Under strict aseptic and antiseptic precautions, subarachnoid block was performed. Patients were made in supine position after completion of block.

There was no change in the patient's position thereafter. The surgical anesthesia was considered effective when T[6-8] dermatome was anaesthetised and bromage grade III block was achieved. Intraoperatively HR, SBP, DBP, RR and SpO_2 were recorded periodically & at the end of procedure patients were shifted to postoperative ward where further haemodynamic monitoring was continued. Observations were made considering following points

1. Onset of sensory block: Time to loss of pinprick sensation at the level of T10 dermatome.
2. Highest level of sensory block and time to attain it were recorded.
3. Time for regression of sensory block by 2 segments was also recorded suggestive of offset of sensory blockade.
4. Onset of motor block: Patient unable to flex knee joint. Motor block was assessed by using modified Bromage scale

Motor block was assessed by modified Bromage score from its onset till achievement of the grade III motor blockade; at the end of surgery and at 30 mins intervals till the patient had no motor block. This time to achieve Grade 0 motor blockade from grade 3 motor blockade was noted & considered as duration of motor blockade. Duration of surgery:

Time to intrathecal injection to end of surgery. (In minutes)

Duration of sensory blockade: Time to sensory onset upto time to S2 regression.

Duration of effective analgesia: It was considered as interval from time of intrathecal injection to the time of 1st analgesic demand post operatively or when VAS score > 4 and at that time inj. tramadol 50 mg i.v. slowly with inj. ondansetron was given as rescue analgesia as per institutional protocol., many institutes use NSAID, but we use Opioid Tramadol for haemodynamic safety.

VAS was managed<4 by analgesic request of inj. tramadol IV 50 mg. Total number of analgesic requests in postoperative 24 hrs were noted. Incidence of complications and side effects Hypotension, Bradycardia, Nausea and vomiting, Respiratory depression, Sedation, Pruritus Shivering, Urinary retention, Post dural puncture headache (PDPH), Transient neurological symptoms (TNS) were noted

- Fall in SBP by more than 30% from baseline value or SBP < 90mmHg. Was considered Hypotension& treated with additional boluses of IV fluids and inj. Ephedrine 6 mg iv was given if hypotension persisted.
- HR < 60/min or fall in HR > 30% from baseline value was considered as Bradycardia, It was treated with 0.6 mg i.v. Atropine. Requirement of alliquotes of atropine in each patient was documented.
- When RR was < 8/min or SpO_2< 90% on room air, it was considered as Respiratory depression. Treated with 100% O_2 via Bain's circuit followed by O_2 through face mask at the rate of 6 L/min.
- Sedation score : Post-operative sedation score was assessed by

OAA score: (chernik et al.) [3]

OAA score was measured by scale of Chernik eta al. Sedation score was noted at 30 mins after SAB upto 6 hours. All the patients were observed for any adverse effects in the postoperative period for 24hrs. Nausea: it was evaluated using a 5 points scale 1– no, 2– mild, 3– moderate, 4– severe, treatment is necessary, 5– intractable, patient complains despite treatment. A rescue antiemetic in the form of iv inj. Ondansetron hydrochloride 4mg stat was given when nausea score was $\geq$ 3.

Requirement of alliquotes of rescue ondansetron on each patient on either group was notified.

Shivering: Grading of shivering was done as per Wrench score. [4] Treatment of shivering carried out with warm fluids and covering of patient and decreasing cooling of OT.

Pruritus: in any patient who began to scratch or who complained of itching, intensity was assessed as Mild – itching was only minor concern, Moderate – itching was a primary concern, although bearable, and the patient said that he/she would itch rather hurt. Severe – unbearable, patient requested treatment. (For severe form of pruritus, antihistaminic inj.

chlorpheneramine maleate was kept ready.) Post dural puncture headache(PDPH) : headache was classified as PDPH if it was aggravated by erect or sitting position, relieved on lying flat, mainly occipital or frontal and increased on coughing, sneezing, or straining. Transient neurological symptoms (TNS): it was defined as pain and / or dysesthenia in the back, buttocks, and legs or pain radiating to lower extremities after initial recovery from spinal anesthesia and resolved within 72 hrs. Patients were followed upto 7 days to check for any other neurological symptoms.

Statistical analysis: The data obtained from MS EXCEL was statistically analysed using suitable SPSS software. Data was expressed as mean +/- SD was compared using unpaired T test. Categorical variables were compared by chi square test. P value <0.05 considered significant (S). and P <0.001 was highly significant. (HS).

P>0.05 wasnon significant.(NS).VAS was explained preoperatively in detailed to the patients and VAS was observed periodically postoperatively. Time to first rescue analgesic request: when VAS Score > 4 rescue analgesic will be given. Total number of analgesic requests in 24 hours noted.

Results

All the patients will undergo routine pre-anaesthetic check-up with necessary investigations.

Table 1: Demographic data

Parameters	Group A (n= 30)	Group B (n=30)	P Value
Age(Year)	38±11.33	34.03±11.22	P>0.05
Height(cm)	167.53±7.9	166.93±7.3	P>0.05
Weight (kg)	54.13±15.8	55.76±15.8	P>0.05
Sex(M/F)	18/ 12	17/13	P>0.05
ASA I/II	19(63.33%) 11(36.66%)	18(60%) 12(40%)	P>0.05
Duration of surgery (min)	129.33±23.9	132.33±24.4	P>0.05

Demographically both groups are comparable.

Haemodynamic, OAA Score and spo2 monitoring: At any time during study, no statistically significant difference was present in HR, SBP, DBP between the two groups. Spo_2 was normal patients were not sedated. OAA score was 5 in each group. (P>0.05). Respiratory rate in both the groups was normal and comparable (P>0.05). No airway interventions were required in each group.

VAS was maintained less than or equal to 4 by rescue analgesia in each group. (p>0.05)

Table 2: Characteristics of sensory motor blockade

Parameters Observed Mean ± SD [In Minutes]	Group A (N=30)	Group B (N=30)	P Value	Inference
Time For Sensory Onset	1.72±0.27	1.68±0.28	P>0.05	Ns
Time For Motor Onset	2.15±0.22	2.12±0.24	P>0.05	Ns
Time For Highest Sensory Block	5.55±0.70	5.54±0.72	P>0.05	Ns
Time For Grade 3	5.57±1.19	5.70±1.27	P>0.05	Ns
Motor Block				
Time To Regression By 2 Dermatome	106.06±10.62	108.26±10.68	P>0.05	Ns
Time For S2 Segment Regression	197.76±7.95	200.8±9.63	P>0.05	Ns
Time For Motor Block To Grade 3-1	184.16±20.55	183.1±17.99	P>0.05	Ns
Time For First Rescue Analgesic	327.83±31.61	501.03±40.22	P<0.001	Hs
Analgesic Request In 24 Hr (No.)	2.83±0.69	1.83±0.74	P<0.05	S

Table 2shows characteristics of spinal block in the two groups. Statistically highly significant difference was present between the two groups for sensory and motor blockade characteristics. (p<0.05)

Adverse Effects: Various adverse effects were notified in both groups. According to Wrench score, grade 1 shivering was noted in 2 patients of group A and 1 patient in group B. Mild pruritus was observed in 1 patient of group A and 2 patients of group B. Nausea and vomiting were noticed in 1 patient of group A and 2 patients of group B. Sedation was not noticed in any patients.

Discussion

With more than 100 years of use, neuraxial anesthesia has gained much success. The ease of performance and versatility of spinal anesthesia has resulted in its widespread popularity. It's a safe and effective alternative to general anesthesia Preservative free Nalbuphine is an opioid drug classified as agonist– antagonist, with mixed μ antagonist and k agonist properties that provide good intraoperative analgesia and prolonged postoperative analgesia with reduced incidence and severity of μ agonist side effects such as pruritus, nausea, vomiting, urine retention, and respiratory depression. Thus, it may become an alternative to other centrally acting opioids such as morphine and fentanyl. [5,6]

However, because of its ceiling effect, which produces a submaximal response compared with an agonist, intrathecal nalbuphine has a shorter duration of analgesia compared with intrathecal morphine. [7,8] Transdermal nitroglycerine has been found to be useful for augmenting the postoperative analgesic effect of intrathecal fentanyl, sufentanyl, clonidine, and neostigmine [7,8,9,10] by release of nitric oxide (NO), which increases the intracellular concentration of cyclic guanosine monophosphate (cGMP). cGMP produces pain modulation in the central and peripheral nervous system [11,12].

Other studies have reported activation of ATP sensitive potassium Chanel's by NO resulting in peripheral antinociception. [13] The synergistic effect of NO when given concomitantly with intrathecal nalbuphine can be attributed to neurons containing NO synthase in laminators 1 of dorsal horn of spinal cord [13] Therefore, we performed this study to determine whether transdermal Nitroglycerine would enhance the analgesic efficacy of intrathecal nalbuphine in patients undergoing lower abdominal procedures under spinal anesthesia. Several studies reported that tNTG patch prolonged post-operative analgesia when combined with various intrathecal adjuvants.

Drug & Dosage: We have taken 3 ml (15 mg) bupivacaine & 1 mg (0.1 ml) preservative free Nalbuphine in both groups. Gupta K et al2 had also taken in their study 3 ml hyperbaric bupivacaine 0.5 % 15 mg & 1 mg of nalbuphine (preservative free) injection made in 0.5 ml normal saline intrathecally. We have also taken similar 1 mg dose of nalbuphine. Mohammad et al [14]. Have used 15 mg 3ml of 0.5% of bupivacaine and 0.8 mg preservative free nalbuphine plus transdermal NTG patch 5 mg applied on chest of the patient, 20 min of spinal anesthesia.

Demographic parameters: Table 1 shows comparable demographic variables (p >0.05) Mohammad et al. [14] comparable demographic parameters.

Hemodynamics characteristics:

HR, SBP, DBP changes in each group were comparable. In both groups hemodynamic variables were stable in intraoperative period. (p> 0.05) No pharmacological intervention required (p > 0.05), were comparable to various studies [11,12,18]

Characteristic of sensory motor blockade: Table 2 shows various characteristics of spinal blockade in each group.

The characteristic of sensory block in our study is more or less similar to other studies with intrathecal preservative free nalbuphine with placebo or transdermal NTG patch used as adjuvants with intrathecal bupivacaine in spinal anesthesia. Parveen S.et al [15] conducted study of intrathecal Nalbuphine; they have concluded that onset of T10 sensory bnset of 1.63± 0.57 min in group Nalbuphine group. Which is highly significant stastically (p < 0.001)? Mohammad HS et al [14] have compared placebo patch and tNTG patch with intrathecal nalbuphine. They also have comparable sensory blockage. (P>0.05) Time to reach highest sensory level, 5.55 ± 0.70 min in group A and 5.54±0.72minutes in group B.(P>0.05)

Gupta K et al [2] studied Intrathecal nalbuphine versus fentanyl as adjuvant to 0.5% hyperbaric bupivacaine for lower limbs surgery & found that time to reach highest sensory level in fentanyl group is 7.4±2.72 min & in nalbuphine group is 7.13±3.81 min which is insignificant statistically (p > 0.05). Mohammad et al [14] have also compared two segment regressions in placebo/ tNTG group .In placebo group it was 158.4±19.1 minutes. And in tNTG group it was 161.2±21.8 minutes. They have observed comparable two segment regression. (p>0.05) Gupta K [2] et al have observed, Two segment regression time for sensory blockade was prolonged in nalbuphine group (118.20 ± 8.56 min.) compared to bupivacaine group (104.56 ± 15.20 min.) (p = 0.001) These findings correlate with our study. Parveenet al [15] found Two segment regression time in nalbuphine group is 99.6±9.86 min and in bupivacaine group is 72.33 ± 9.35 min (p < 0.001) . So adding Nalbuphine to hyperbaric bupivacaine is definitely advantageous. Time to regression by S2 dermatome (min) in group A is 197.76 ± 7.95 min. and group B is 200.8±9.63 min. which is non-significant. (p >0.05) Patwa et al [1] concluded that duration of sensory blockade is 153.33 ± 25.33 min in bupivacaine group and 242.5±22.46 min in nalbuphine group which is highly significant statistically (p < 0.001), similar to our study.

Time to motor regression from bromage 3-1 is 184.16±20.55 min in group A and 183.1±17.99 min. in group B,. (p > 0.05) Mohammad et al [14] have total duration of motor blockage, in placebo group 276.3 ±16.8minutes and in tNTG group it was 274.7± 15.3 minutes. Patwa.et al1study results are also comparable to our study for intrathecal Nalbuphine with placebo group.

Time of 1st rescue analgesia (min) in group A is 327.83 ± 31.61 min and group B is 501.03 ± 40.22 min which is highly significant stastically. (p <0.001) .Application of transdermal nitroglycerine patch 5 mg prolonged postoperative analgesia following intrathecal nalbuphine and negates its ceiling analgesic effect. This synergistic effect is mediated through the release of NO. The mechanism by which NO enhances analgesia is not clear. NO is an important messenger in tonic cholinergic inhibition of pain 12 NO-cyclic monophosphate (C-GMP) cascade is involved in acetylcholine or morphineinduced peripheral antinociception[16] NO is involved in the activation of descending pain pathways through activation of C-GMP13 Other studies have reported the activation of ATP-sensitive potassium channels by NO, resulting in peripheral antinociception [17].

The synergistic effect of NO when given concomitantly with intrathecal nalbuphine can be attributed to neurons containing NO synthase in lamina I of dorsal horn of spinal cord [18]. Mohammad HS et al [14] have time to first rescue analgesia in placebo group 334.2 ±15.6minutes and in tNTG group it was 482.6 ± 16.3 minute (p<0.001) Gupta K et al [2] have concluded that duration of postoperative analgesia was 6-8 hrs in nalbuphine group compared to 3-4 hrs in bupivacaine group, (p = 0.0001). These findings correlate with our study. Parveenet al [15] shown that duration of effective analgesia is 420.4 ± 25.30 min in nalbuphine group and 170.83 ± 27.59 min in bupivacaine group. (p < 0.001).

Total analgesic request in 24 hrs in group A is 2.83±0.69 min, group B is 1.83±0.74 min (p < 0.05). Mohammad et al [14] have calculated total dose of intra muscular ketorolac in 24 hours it was 84.2 mg in placebo patch group and 40.1 mg in tNTG patch group.(P<0.001)

Adverse effects:

Shivering was observed in 3.33% patients of group A and Nill in group B. Pruritis was observed in 6.66% of group A and nill in group B. Nausea and vomiting were observed in, 6.66% of group A and 3.33% in group B.

Respiratory depression and bradycardia and hypotension were not observed in any group.

PDPH and TNS symptoms were not observed in any group.

Mohammad al [14] have also studied about side effects in both groups and showed that both group have minimum side effects.

Culebra X.et al [19] had observed dose dependent incidence of pruritus and nausea vomiting. ($p< 0.05$). Parveen et al [15] has observed no hemodynamic and respiratory adverse effect in nalbuphine group.

Regarding PDPH and TNS our observations correlate with study of Mohammad et al [14]

Limitations:

1. We have used same drug bupivacaine in same concentration 15 mg with Nalbuphine 1 mg as adjuvantin both groups.
2. We have no group allocated in which only spinal bupivacaine given & t NTG patch applied.
3. Future Recommendations: Different doses of Nalbuphine with spinal bupivacaine along with tNTG patch as coadjuvant should be explored.

Conclusion

In Nutshell transdermal NTG is good Co-adjuvant to intrathecal preservative free nalbuphine 1mg with hyperbaric bupivacaine (15mg) as it provides perioperative hemodynamic stability and potentiate duration of postoperative analgesia, decreases 24 hours requirement of rescue analgesia with minimum adverse effects.

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