Deori *et al.*
Ain-Shams Journal of Anesthesiology (2023) 15:83
https://doi.org/10.1186/s42077-023-00382-y

Ain-Shams Journal of Anesthesiology

ORIGINAL ARTICLE

Open Access

Comparative study on regression time of block and adverse effects of nalbuphine and fentanyl as an adjuvant to intrathecal bupivacaine: a prospective randomized double-blind study

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Abstract

Background The study was done to observe the effectiveness of nalbuphine as an adjuvant to intrathecal bupivacaine heavy, and hence, it was compared in terms of regression time of sensory and motor block and adverse effects with that of fentanyl as an adjuvant. The study design was a prospective randomized double-blind study. Total number of patients were 100. They were randomly allocated into two groups. Group N ($n = 50$) received 3.2 ml of 0.5% heavy bupivacaine and 0.5 ml (0.8 mg) of nalbuphine, a total of 3.7 ml. Group F ($n = 50$) received 3.2 ml of 0.5% heavy bupivacaine and 0.5 ml (25 µg) of fentanyl, a total of 3.7 ml. Assessment of sensory and motor blockade and analgesia was done by visual analogue scale and modified Bromage scale.

Results On comparing the spinal block characteristics among two groups to reach, Bromage-3 motor block was found to be significantly shorter in group F ($p = 0.03777$). The regression time of both sensory and motor block was significantly prolonged in group N ($P < 0.0001$). No patients required additional analgesic intraoperatively, and intraoperative VAS scores and adverse effects were comparable in the two groups.

Conclusions On comparing nalbuphine 0.8 mg and fentanyl 25 µg as an adjuvant to intrathecal bupivacaine, it has been observed that nalbuphine significantly prolongs regression time of sensory and motor block indicating the effectiveness of nalbuphine as an alternative to fentanyl and for prolong surgeries. The incidence of adverse effects was similar in both groups.

Keywords Nalbuphine, Fentanyl, Hyperbaric bupivacaine, Nalbuphine prolongs block

Background

A common problem during intra-abdominal surgery under spinal anaesthesia is visceral pain and epigastric and chest discomfort along with nausea, vomiting, hypotension, and bradycardia (Mohamed et al. 2021). Fentanyl has been used as an adjuvant to reduce epigastric and chest discomfort along with to intensify analgesia. Nalbuphine is a relatively new agonist-antagonist opioid to use as an adjunct (Seewal et al. 2007). Nalbuphine has lesser abuse potential and respiratory depressant effect compared to fentanyl. Nalbuphine is not, but fentanyl is a regulated drug in India. The study aimed to determine whether nalbuphine or fentanyl prolongs regression time from the optimal block when used as an adjuvant with

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hyperbaric bupivacaine 0.5% along with their possible adverse effects (Yan et al. 2019).

Methods

The study design was a prospective randomized double-blind study conducted in a government tertiary care hospital in India. The study was conducted on patients with spinal anaesthesia with bupivacaine heavy forming two groups: group 1 with nalbuphine and group 2 with fentanyl as an adjuvant. The two groups were compared for regression time from the optimal block as the primary outcome and adverse effect as the secondary outcome.

Inclusion criteria were patient's approval, age group 20–60 years, ASA grades I and II physical status, elective lower abdominal, and gynaecological surgeries. Exclusion criteria were contraindication to regional anaesthesia like bleeding disorder, ASA grades III and IV physical status, uncontrolled hypertension, diabetes mellitus, psychic disorder, chronic low back pain, and alpha- and beta-blocker treatment.

All patients received tab ranitidine 150 mg on the night before and the morning of the day of surgery. Intravenous ondansetron was given 1 h before surgery. All drug solutions were prepared by an anaesthesiologist who was not involved in the administration of anaesthesia, patient care, and data collection. The total number of patients were 100. They were randomly divided into two groups of fifty each using computer-generated randomized numbers. Group N ($n = 50$) received 3.2 ml of 0.5% heavy bupivacaine and 0.5 ml (0.8mg) of nalbuphine, a total of 3.7 ml. One millilitre of nalbuphine contains 10 mg of nalbuphine. This 1-ml nalbuphine was made to 5 ml by adding 4 ml of NS. Now, each millilitre would contain 2 mg. Four millilitres of this diluted solution was taken and made 5 ml by adding NS. The resultant solution would contain nalbuphine 1.6 mg per ml. From this solution, 0.5 ml (0.8) was taken for intrathecal injection. Group F ($n = 50$) received 3.2 ml of 0.5% heavy bupivacaine and 0.5 ml (25 μg) of fentanyl, a total of 3.7 ml. One ample fentanyl contained 100 μg in 2-ml solution. So, 0.5 ml will contain 25 μg.

On arrival in the OT, all routine monitors were applied, and baseline measurements were recorded. An IV line with lactate Ringer's solution through an 18-g cannula was started. Patients were instructed about visual analogue score (VAS) on a scale of 10-cm length with 0 corresponding to "no pain" and 10 maximum intolerable pain experienced.

The patients were placed in the left lateral position. Intrathecal injections were done with Quincke's point needle in the L3–L4 interspaces. Patients in group N received 3.2 ml of bupivacaine and nalbuphine. Those in group F received 3.2 ml of bupivacaine and fentanyl intrathecally. The anaesthetist administering the drugs as well as the patients was blinded to the group allocation. The patients were placed supine position following the subarachnoid block. The sensory level of the block was assessed bilaterally in the axillary line by loss of pinprick sensation, by using a short bevelled 25-gauge needle.

Assessment of sensory blockade

The sensory block was assessed by a pinprick of the skin using a hypodermic needle every 2 min until the level stabilized for 3 consecutive tests since the intrathecal injection of the drugs was defined as the time for the spinal block to the highest sensory dermatome level. Similarly, patients were tested every 15 min until the sensory block regressed two segments from the highest level of sensory block attained and then every 30 min until the patient first complained of pain.

Assessment of analgesia: visual analogue cale

VAS score	Intensity of pain
0–2	No pain to slight pain
2–5	Mild pain
5–7	Moderate pain
7–9	Severe pain
10	Worst possible pain

Assessment of motor block: modified Bromage scale

- Grade 0—Full flexion of knees and feet
- Grade 1—Just able to flex knees and full flexion of the feet
- Grade 2—Unable to flex knees but some flexion of the feet
- Grade 3—Unable to move legs or feet

Motor blockade was assessed every 2 min until the lower limb block reached Bromage 3 and then every 15 min until the lower limb block regressed to Bromage 0. The time to reach Bromage 3 from the time of the intrathecal injection of drugs was noted. The time of regression to Bromage 0 was also noted.

Hypotension was defined as a 20% decrease in mean arterial pressure from the baseline value. It was treated with boluses of 6-mg mephentermine. Bradycardia was defined as a pulse rate of less than 60/min and was treated with intravenous atropine 0.6 mg. Adverse effects observed were nausea and vomiting, pruritus, bradycardia, hypotension, shivering, and respiratory depression.

Statistical analysis was done with GraphPad InStat R3 statistical software. For qualitative data, chi-square test

Table 1 Demographic characteristics

Variables	Group *N*	Group *F*	*p*-value
Age (year)	41.02 ± 8.874	42.04 ± 9.500	0.05
Male/female	46%	48%	1.000
Weight (kg)	62.28 ± 8.412	63.28 ± 8.286	0.5349
Height (cm)	154.98 ± 8.606	155.28 ± 8.379	0.860
Duration of op (min)	112.9 ± 9.208	111.76 ± 8.146	0.05

was used. Quantitative data were analysed using a Student *t*-test. Pearson chi-square test was done to calculate the *p*-value for incidences of various adverse effects in each group. From previous studies assuming a study power of 80% and a probability of type 1 error of 5%, a sample size of 100 patients was found to be required for obtaining a statistically significant mean difference in the mean duration of analgesia in two groups. Hence, assuming an equal distribution of patients in both groups, a total number of 50 patients were taken in each group.

Results

A total of 100 patients were taken for the research study. Demographic characteristics, duration, and types of surgeries were identical. Baseline vital parameters were comparable between both groups (Table 1).

On comparing the spinal block characteristics among the two groups after applying an unpaired *t*-test (Welch corrected), it was noticed that there was no significant difference in the onset of sensory block and the highest level of sensory block attained. The time to reach the Bromage-3 motor block was found to be significantly shorter in group F ($p = 0.03777$). The regression time of both sensory and motor blocks was significantly prolonged in group N ($p \leq 0.0001$). The mean regression time to the S1 dermatome level was significantly longer in group N than in group F (*P*-value ≤ 0.0001); also, mean regression time to reach Bromage 0 in group N was extremely prolonged than that of group F (*P*-value ≤ 0.0001) (Table 2).

No patients required additional analgesic intraoperatively, and intraoperative VAS scores were comparable in the two groups. The mean VAS score in the 2nd hour was 0.4041 in group N and 0.3734 in group F with a *P*-value of 0.6397, and at the end of the 24th h, VAS was 0.4015 in group N and 0.4353 in group F with *P*-value of 0.8403, indicating no significant difference between the two groups (Table 3).

Incidences of adverse effects were insignificant in both groups. *P*-values evaluated for adverse effects, namely nausea, vomiting, pruritus, bradycardia, hypotension, shivering, urinary retention, and respiratory depression were 0.6464, 0.6186, 0.3194, 0.6464, 0.6951, 0.6186, 0.00, and 0.00, respectively (Table 4).

Table 3 VAS score

VAS score	Group	Mean	*SD*	*p*-value
1 h	Group N Group F	0.00 0.00	0.0 0.0	
2nd h	Group N Group F	0.2 0.16	0.4.41 03734	0.6397
3rd h	Group N Group F	0.3 0.22	04629 0.4185	0.3669
4th h	Group N Group F	2.112 2.178	04861 0.6231	0.5562
6th h	Group N Group F	2.126 2.068	0.2094 0.1987	0.1571
12th h	Group N Group F	3.082 2.988	0.4035 0.3260	0.2018

Table 4 Incidences of adverse effects

Adverse effect	Group	Incidence	*p*-value
Nausea & vomiting	N F	5 (10%) 4 (8%)	0.6400
Pruritus	N F	0 1	0.3194
Bradycardia	N F	2 3	0.6464
Hypotension	N F	3 4	0.6951
Shivering	N F	3 1	0.6186
Respiratory depression	N F	0 0	

Table 2 Subarachnoid block characteristics

	Group *N*	Group *F*	*p*-value
Time to reach T 10 sensory block level	4.264 ± 0.625 min	4.076 ± 0.7558	0.1785
Time to reach Bromage-3 motor block	5.334 ± 0.4138 min	5.136 ± 0.5201 min	0.0377*
Regression time to S1 dermatome level	167.62 ± 16.217 min	141.34 ± 14,400 min	< 0.0001*
Regression time to reach Bromage-0	233.5 ± 9.049 min	114.34 ± 14.40 MIN	< 0 .0001*

Discussion

Bowel and chest discomfort along with nausea during lower abdominal surgeries like caesarean section and appendicectomy, etc. are well-known adverse effects of spinal anaesthesia. Adjunct like fentanyl and nalbuphine to intrathecal bupivacaine is effective in handling those patient discomfort. This study was conducted to observe how effectively those adjuncts help in achieving effective block with minimal adverse effects.

On comparing the spinal block characteristics among the two groups, it was noticed that there was no significant difference in the onset of sensory block and the highest level of sensory block attained. The time to reach the Bromage-3 motor block was found to be significantly shorter in group F ($P = 0.03777$). The regression time of both sensory and motor block was significantly prolonged in group N ($P < 0.0001$) (Table 2). Intrathecal opioids cause analgesia by binding to an opioid receptor in the dorsal horn of the spinal cord. Opioids were the first and foremost agent to attain an integral role as a spinal anaesthetic adjuvant. Kuusniemi et al. (2000) and Indurkar et al (2017) found that fentanyl 25 mg was most effective. Hamber et al. in a review article concluded that fentanyl in doses of 20–30 μg as an adjunct to spinal anaesthesia produces faster improved intraoperative analgesia and decreased incidence of intraoperative nausea and vomiting in obstetric patients (Bernards 2005; Gonzalez-Coda et al. 2014; Rahman et al. 2022; Singh et al. 2015). Nalbuphine is a highly lipid-soluble opioid having agonist action at K-opioid receptors and antagonist activity to the μ-opioid receptors. Gupta, Kumkum et al. concluded that intrathecal nalbuphine 0.8 mg proved good for intraoperative and early postoperative analgesia without side effects (Ebrie et al. 2022; Gupta et al. 2016). Adding nalbuphine 1.6 mg to bupivacaine did not increase efficacy but increased the incidence of complications. Nalbuphine and other agonists have reasonably potent analgesia in certain models of visceral nociception (Hambe and Viscomi 1999).

In the present study, mean time of onset of analgesia in the two groups was similar. The result was consistent with Lee et al. and Patwaa et al. (2011, 2014). The highest level of sensory block achieved in the present study was T4 in both groups. The time for sensory regression to S1 was significantly longer in group N compared to group F. Gupta, Kumkum et al. also found nalbuphine to be longer acting than fentanyl (Gupta et al. 2016). In the present study, the time of onset of grade III motor blockade was not statistically different in the two groups. Lee, Patwaa A. A. et al. and Abdolreza et al. found no difference in the onset of Bromage-3 motor block between the two groups (Anaraki et al. 2012; Lee et al. 2011; Patwaa et al. 2014). The regression time to reach Bromage 0 motor block in the nalbuphine group was significantly longer than in the fentanyl group. Though we prefer spinal anaesthesia for early ambulation in cases like Lscs or other short surgeries, there are some complicated situations where the surgeon needs to prolong sensory and motor block.

In the present study, no patients required additional analgesia intraoperatively and the VAS score was comparable in both the study groups (Table 2) Findings were consistent with other studies (Alahuhta et al. 1990; Faure et al. 1982; Fernandez-Galinski et al. 1996).

We found that the adverse effects like nausea, vomiting, pruritus, shivering, bradycardia, hypotension, and respiratory depression were found to be very low, and differences were insignificant between the two groups as in other studies (Table 3) (Al-Ghanem et al. 2009; Culebras et al. 2000; Prabhakaraiah et al. 2017).

Limitations of our study were that we did not have a control group; sedation score was obliterated because of confusing findings. Even though nalbuphine over score fentanyl in certain findings, it fails to get a significant advantage over fentanyl needing further evaluation.

Conclusions

On comparing nalbuphine 0.8 mg and fentanyl 25 μg as an adjuvant to intrathecal bupivacaine, it has been observed that nalbuphine significantly prolongs the regression time of sensory and motor block indicating the effectiveness of nalbuphine as an alternative to fentanyl and for prolong lower abdominal surgeries. The incidence of adverse effects was similar in both groups.

Abbreviations

ASA	American Society of Anaesthesiologist
Group N	Nalbuphine
Group F	Fentanyl
IV	Intravenous
NS	Normal saline
VAS	Visual analogue scale

Acknowledgements

The authors would like to acknowledge help and cooperation of all participants and guardians, operating room technicians, nurses, and residents of Anaesthesia and Critical Care Department, SMCH, Silchar, Assam, India.

Authors' contributions

Concepts, clinical study, and experimental studies by KCD. Design, data analysis, manuscript preparation, and manuscript editing by MKT. Definition of intellectual content, manuscript review, and guarantor by KCD, MKT, and BL.

Funding

The study was self-sponsored, and no funding was done for the study.

Availability of data and materials

All the data generated in the present study is not publicly available but will be made available on demand from corresponding author.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional ethics committee of SMCH. Taking part in this study voluntarily, patient may choose not to take part in this study, or if he/she decides to take part, patient can later change mind and withdraw from study. The patient's decision will not change the present or future health care or other services that he/she receives. The study doctor may stop participation in this study anytime. Patients bore the cost of investigations as per SMCH guidelines. All information collected about patients will be kept confidential to the extent permitted by law. The code number will be used for patient's identification in this record. The information from this study may be published, but patients' identity will be kept confidential in any publication.

Consent for publication

Informed consent for study publication is taken from all participants in writing.

Competing interests

The authors declare that they have no competing interests.

Received: 3 March 2023 Accepted: 12 October 2023
Published online: 26 October 2023

References

Alahuhta S, Kangas-Saarela T, Hollmen AL, Edstrom HH (1990) Visceral pain during caesarean section under spinal and epidural anaesthesia with bupivacaine. Acta Anaesthesiol Scand 34:95–8

Al-Ghanem SM, Massad IM, Al- Mustafa MM et al (2009) Effect of adding dexmedetomidine versus fentanyl to intrathecal bupivacaine on spinal block characteristic in gynaecological procedure; a double-blind control study. Am JpplSci 6:882–7

Anaraki AN, Abbasi M, Anvarypour A, Motamed N (2012) The effects of adding meperidine to heavy intrathecal lidocaine on hemodynamic changes and blood loss in open prostatectomy: a randomized double-blind clinical trial. IJMS 37(1):15

Bernards CM (2005) Sophistry in medicine: lessons from the epidural space. Reg Anesth Pain Med 36:56–66

Culebras X, Gaggero G, Zatloukal J et al (2000) Advantages of intrathecal nalbuphine, compared with intrathecal morphine, after caesarean delivery: an evaluation of postoperative analgesia and adverse effect. Anesth Analg 91(3):601–605

Ebrie AM, Woldeyohanis M, Abafita BJ, Ali SA et al (2022) Hemodynamic and analgesic effect of intrathecal fentanyl with bupivacaine in patients undergoing elective cesarean section; a prospective cohort study. PLoS One 17(7):e0268318

Faure E, Wittels B, Klafta J, Toledano A et al (1982) Intrathecal nalbuphine with fentanyl for labour analgesia. Br J Anaesth 54:479–86

Fernandez-Galinski D, Rue M, Moral V et al (1996) Spinal anaesthesia with bupivacaine and fentanyl in geriatric patients. Anesth Analg 83(3):537–41

Gonzalez-Coda A, Amasha R, Yaksh TL (2014) Spinal anaesthesia adjuvant, American Society of Regional Anaesthesia and pain medicine

Gupta K, Rastogi B, Gupta PK et al (2016) Intrathecal nalbuphine versus intrathecal fentanyl as an adjuvant to 0.5% hyperbaric bupivacaine for orthopaedic surgery of lower limbs under subarachnoid block: a comparative evaluation. Indian J Pain 30(2):90–95

Hambe EA, Viscomi CM (1999) Intrathecal lipophilic opioids as an adjunct to surgical spinal anaesthesia. Reg Anesth Pain Med 24(3):255–63

Indurkar PS, Saibaba S (2017) A comparative study of hyperbaric bupivacaine versus hyperbaric bupivacaine and fentanyl (12.5 mcg) in subarachnoid anaesthesia for lower abdominal and lower extremity surgeries. Int J Res Med Sci 3(11):3147–3155

Kuusniemi KS, Pihlajamaki KK, Pitkanen MT et al (2000) The use of bupivacaine and fentanyl for spinal anaesthesia for urologic surgery. Anesth Analg 91:1452

Lee JH, Chung KH, Lee JY, Chun DH, Yang HJ, Ko TK, Yun WS (2011) Comparison of fentanyl and sufentanil added to 0.5% hyperbaric bupivacaine for spinal anaesthesia in patients undergoing cesarean section. Korean J Anesthesiol 60(2):103–8

Mohamed SA, Elsonbaty A, Elsonbaty M (2021) A comparison between intrathecal nalbuphine and fentanyl for intraoperative pain management during uterine exteriorization in cesarean section: a randomized controlled trial. Open Access Maced J Med Sci 9:533–540

Patwaa AA, Endijeri A, Upadhyay MR (2014) A comparison of intrathecal nalbuphine hydrochloride with hyperbaric bupivacaine 0.5% and hyperbaric bupivacaine 0.5% alone in patients undergoing abdominal hysterectomy. Int J Res Med 3(2):7–11

Prabhakaraiah UN, Narayanappa AB, Gurulingaswamy S, Kempegowda K, Vijaynagar KA, Hanumantharayappa NB (2017) "Comparison of nalbuphine hydrochloride and fentanyl as an adjuvant to bupivacaine for spinal anesthesia in lower abdominal surgeries:" a randomized, double-blind study. Anesth Essays Res 11(4):859–863

Rahman MM, Rasheduzzaman M, Kabir K, Amin W, Debnath PK, Kabir MS et al (2022) Intrathecal fentanyl to bupivacaine intensify sensory and motor block without prolonging recovery time for urosurgeries. EAS J Anesthesiol Crit Care 4(2):27–31. https://doi.org/10.36349/easjacc.2022.v04i02.004

Seewal R, Shende D, Kashyap L et al (2007) Effect of addition of various doses of fentanyl intrathecally to 0.5% hyperbaric bupivacaine on perioperative analgesia and subarachnoid block characteristic in lower abdominal surgery. A dose-response study. RegAnesth Pain Med 32(1):20–6

Singh R, Kundra S, Gupta S, Grewal A, Tewari A (2015) Effect of clonidine and/or fentanyl in combination with intrathecal bupivacaine for lower limb surgery. J Anaesthesiol Clin Pharmacol 31(4):485–90

Yan W, Xiong Y, Yao Y et al (2019) Continuous intravenous infusion of remifentanil improves the experience of parturients undergoing repeated cesarean section under epidural anaesthesia, a prospective, randomized study. BMC Anesthesiol 19:243

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