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Original Research Article

A prospective, randomized, double blind, comparative study of intramuscular nalbuphine hydrochloride, butorphanol tartrate and pentazocine lactate for post-operative pain relief following abdominal hysterectomy

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ABSTRACT

Background: This study aimed to compare the efficacy and safety of intramuscularly administered nalbuphine, butorphanol and pentazocine for post-operative pain relief after abdominal hysterectomy.
Methods: Seventy-five adult female patients, aged between 20-50 years, belonging to American Society of Anaesthesiologists (ASA) class 1 and 2, posted for abdominal hysterectomy under spinal anesthesia were included in the study. The subjects were randomly divided into 3 groups (n=25 each) and given – Group A: pentazocine lactate (30 mg, 1mL), Group B: butorphanol tartarate (2 mg, 1 ml) and Group C: nalbuphine hydrochloride (10 mg, 1 mL) when post-operative pain intensity reached ≥4 mm on the Visual analogue scale (VAS). The onset, duration, time to peak effect and adverse events were recorded at regular intervals for 24 hours, postoperatively.
Results: The mean time to onset of anesthesia was significantly faster ($P<0.05$ each) in the nalbuphine (10.2±2.2 minutes) and butorphanol (11.3±2 minutes) groups when compared to the pentazocine group (14±2.7 minutes). Duration of analgesic action was significantly longer ($P<0.05$ each) in the nalbuphine (236.4±75.1 minutes) and butorphanol (202±59.2 minutes) groups when compared to the pentazocine group (177.4±55.3 minutes). No significant differences in respiratory and cardiovascular parameters were noted between the groups. Nausea and vomiting was seen significantly higher in the pentazocine group (36%) when compared to butorphanol (20%) and nalbuphine (8%) groups ($p<0.05$ each).
Conclusions: Intramuscular nalbuphine and butorphanol provided effective analgesia with rapid onset and longer duration of action, with lower incidence of nausea and vomiting when compared to pentazocine. In particular, nalbuphine can be a suitable agent to provide post-operative pain relief in gynecologic lower abdominal surgery.

Keywords: Analgesia, Butorphanol, Nalbuphine, Pentazocine, Surgery

INTRODUCTION

Effective postoperative pain management plays a significant role in modern day surgical practice. Providing good analgesia during the postoperative period not only plays a compassionate role, but also results in additional medical and economic advantages. These benefits include increased patient comfort, quicker mobilization, lesser risk of deep vein thrombosis, decreased risk for neuropathic pain, speedy recovery and discharge from hospital with reduced hospital costs.[1,2]

Opioids are one of the first-line agents used in the management of postoperative pain.[3,4] Currently available opioid analgesics differ in their pharmacological actions and tolerability. Many protocols and recommended standard doses have been used. They offer good analgesic

efficacy, but have a narrow therapeutic window due to the risk of adverse effects such as respiratory depression, drowsiness, nausea, vomiting, miosis, dizziness and constipation.[5]

The agonist-antagonist opioid analgesics pentazocine, butorphanol and nalbuphine are weak antagonists of mu-receptors and partial kappa-agonists. All the three have strong analgesic action when given by injection route, lower propensity to cause respiratory depression and a lower potential for abuse when compared with pure opioid analgesic like morphine.[6]

In the postoperative period, it is crucial that the agents used have a fast onset and long duration of action with a wide safety margin. The aim of this study was to compare the efficacy and safety of a single equianalgesic dose of nalbuphine, butorphanol and pentazocine given by intramuscular injection for post-operative pain management in lower abdominal surgery (abdominal hysterectomy) conducted under spinal anesthesia with local anesthetic bupivacaine.

METHODS

This was a prospective, randomized, double-blind, active-controlled, single-dose, three-groups comparison study with two test groups (nalbuphine hydrochloride and butorphanol tartrate) and one active control group (pentazocine lactate) conducted at the Government General Hospital, Rangaraya Medical College, Andhra Pradesh, India between March 2010 to February 2011 The Institutional ethics committee attached to the hospital approved the protocol and other study documents. The study was conducted in compliance with the ethical principles outlined in the declaration of Helsinki and following the good clinical practice (GCP) guidelines. Seventy-five (75) female patients posted for elective total abdominal hysterectomy surgery under spinal anesthesia were randomly allocated to three groups of 25 patients each, to receive pentazocine lactate (Group A), butorphanol tartrate (Group B) or nalbuphine hydrochloride (Group C). Randomization was done using table of random numbers and allocation concealment to the three groups (A, B, C) was done by enclosing the assignments in serially numbered sealed opaque envelopes.

The study included female patients aged between 20-50 years, American Society of Anaesthesiologists (ASA) grade I or II posted for abdominal hysterectomy under spinal anesthesia. Patients with hypertension, diabetes mellitus, asthma, cardiac diseases, coagulopathies (or on anticoagulant drugs), impaired hepatic or renal functions, chronic alcohol dependence, systemic infections, and any contraindication to spinal anesthesia were excluded from the study. Patients with history of hypersensitivity, dependence or tolerance to opioids were also excluded from the study.

Detailed history and physical examination was performed on all patients pre-operatively. Clinical investigations performed included complete blood count, blood glucose, blood urea, serum creatinine, urine routine analysis, chest X-ray, electrocardiogram and abdominal ultrasound. Patients were explained about the study procedures including the anaesthetics techniques and about the visual analogue scale (VAS) used to record pain (Figure 1). All patients were pre-medicated with alprazolam 0.5mg orally on previous night of surgery and injection midazolam (2-3mg) given intravenously before anaesthesia. All the patients received spinal anaesthesia with 2-3 mL of injection bupivacaine 0.5% heavy for their surgical procedure (Figure 1).

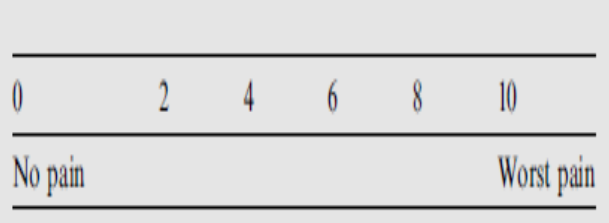

Figure 1: Visual analogue score VAS (0-10 cm).

Assessment of pain was done in the recovery room/post-operative ward. The score on VAS was evaluated every 15 minutes for first one and half hour; every 30 minutes up to 6 hours and subsequently two hourly till 24 hour. Only patients whose VAS score was ≥40 mm were included in the study and the test drug was administered intramuscularly with the help of nursing staff, who were otherwise uninvolved in the study. The nurse opened serially numbered envelop and determined the group (A, B, C) to which the patient was allotted. The medications were labeled A (pentazocine lactate 30mg, 1mL), B (butorphanol tartarate 2mg, 1ml) and C (nalbuphine hydrochloride 10mg, 1mL). The nurse administered the study drug as an intramuscular injection and recorded the assigned group and time of administration in the case report form. After administration of this single dose of the study analgesic, rescue analgesic in the form of injection diclofenac sodium (75mg, intramuscular) was used when VAS score reached ≥40 mm again or on patient demand for analgesia.

Analgesic efficacy measures included onset of action, duration of action, and time to peak effect. Onset of action was defined as time taken for VAS to reduce to less than 4 mm after the injection of the study analgesic. Peak effect was defined as time taken for VAS to reach 0. Duration of action was defined as time from administration of study drug to administration of rescue analgesic during the study duration.

Pulse rate, blood pressure and respiratory rate were recorded every 5 minutes for first 30 minutes, then every 30 minutes for 2 hours, then hourly until 4 hours, then fourth hourly for 24 hours. Subjects were monitored for side effects such as nausea, vomiting, pruritus and

respiratory depression. Sedation was assessed with Wilson Sedation Scale (Table 1) at 1 hour, 2 hours, and 4 hours after analgesic injection. After the study duration of 24 hours, patients were moved to their wards and placed on post-operative analgesic therapy as per hospital standards (Table 1).

Table 1: Wilson sedation scale.

Score	Description
1	Fully awake and oriented
2	Drowsy
3	Eyes closed but arousable to command
4	Eyes closed but arousable to mild physical stimulation (earlobe tug)
5	Eyes closed but unarousable to mild physical stimulation

Data was analyzed using the Statistical Package for Social Sciences (SPSS) for Windows, version 17.0 (SPSS Inc, Chicago). Simple descriptive statistics was used to present the demographic characteristics of the study participants. Continuous variables are presented as mean ± standard deviation. Efficacy parameters were analyzed using paired 't' test and Chi-square (χ^2) tests was used to compare categorical variables. The incidence and frequency of adverse events have been reported. All statistical tests were 2-sided, and p value <0.05 was considered as a significant difference.

RESULTS

Baseline demographics and surgery details were as presented in Table 2. The three study groups were comparable on the parameters of age, height, weight, ASA grades and surgical procedures. In all the three groups of patients, hemodynamic parameters remained within normal limits during the surgery (Table 2).

Table 2: Demographic features of study population.

	Pentazocine (N=25)	Butorphanol (N=25)	Nalbuphine (N=25)
Age, years	44.3 (±5.8)	43.5 (±7.9)	43 (±6.5)
Weight, kg	51.0 (±5.3)	49.9 (±4.8)	49.1(±3.9)
Height, cm	153.28 (±2.68)	155.32 (±4.88)	154.96 (±4.65)
ASA grades 1/ 2, n	23,2	22,3	23,2
Total operating time, minutes	75.6 (±23.4)	78.2 (± 20.4)	73.3(± 25.8)
Data has been presented as Mean (±SD)			

Mean VAS at the time of administration of analgesic in the pentazocine, butorphanol and nalbuphine groups were 7.40, 7.61, and 7.34, respectively (not statistically different). Onset of analgesic action was fastest in the nalbuphine group within 10.2 minutes (range 7-15 minutes); while it was 11.3 minutes (range 8-16 minutes) in the butorphanol group and 14 minutes (range 9-20 minutes) in the pentazocine group (Table 3). The onset of action was significantly faster in the nalbuphine and butorphanol groups (P<0.05 each) when compared to the pentazocine group. The difference in onset of action between nalbuphine and butorphanol group was not statistically significant (Table 3).

Mean duration of analgesic action was almost four hours (236.4 minutes) in the nalbuphine group (range 120-360 minutes), when compared to 202 minutes in the butorphanol group (range 90-330 minutes), and 177.4 minutes (range 75-300 minutes) in the pentazocine group (Table 3). The duration of analgesic action was significantly higher in the nalbuphine and butorphanol group (P<0.01 each), when compared to the pentazocine group. Duration of action was not statistically different between the nalbuphine and butorphanol groups.

Peak effect was observed in the nalbuphine group at a mean duration of 39 minutes (range 30-60 minutes); while the same was seen in 58.8 minutes (range 45-75 minutes) in the butorphanol group and in 70.8 minutes (60 -90 minutes) in the pentazocine group (Table 3). Both the test groups achieved peak effect at significantly lower time (P<0.01) when compared to the pentazocine group. Nalbuphine group had a significantly quicker onset of peak effect when compare to butorphanol group (P<0.01).

Table 3: Comparison of analgesic effects.

	Pentazocine (N=25)	Butorphanol (N=25)	Nalbuphine (N=25)
VAS at time of administration	7.4 (0.6)	7.61 (0.5)	7.34 (0.7)
Onset of action (min)	14 (2.7)	11.3 (2) *	10.2 (2.2) *
Onset of Peak action (min)	70.8 (10.1)	58.8 (10.5)**	39 (10.6)**
Duration of action (min)	177.4 (55.3)	202 (59.2) **	236.4 (75.1)**
* = p <0.05 vs. Active Control (pentazocine) - significant ** = p <0.01 vs. Active Control (pentazocine) - highly significant			

No significant between-group difference was noted in the cardiovascular parameters monitored including heart rate, systolic BP and Diastolic BP. No significant differences were seen between groups in the respiratory parameters monitored such as respiratory rate and SpO_2.

Levels of sedation at different time points after analgesic injection is presented in Table 4. None of the patients reached sedation score 4 or 5 in any groups. At one hour after administration of analgesic, a higher proportion were awake (Wilson Score 1) in the nalbuphine group

(76%), than in the pentazocine (68%) and butorphanol (44%) groups. There was a significant difference between nalbuphine and butorphanol group with respect to those awake at 1 hour (P=0.021) (Table 4).

Table 4: Post-operative sedation.

	1 hour					2 hours					4 hours				
Sedation score	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Pentazocine (N=25)	17	6	2	0	0	20	5	0	0	0	23	2	0	0	0
Butorphanol (N=25)	11	8	6	0	0	18	7	0	0	0	21	4	0	0	0
Nalbuphine (N=25)	19	5	1	0	0	21	4	0	0	0	22	3	0	0	0

Table 5: Adverse effects noted in the study.

	Pentazocine (N=25)	Butorphanol (N=25)	Nalbuphine (N=25)	Total (N=75)
Nausea and vomiting	9 (36%)	5 (20%)	2 (8%)	16 (21.3%)
Headache	1 (4%)	0	0	1 (1.3%)
Shivering	0	0	1(4%)	1 (1.3%)

The adverse events noted in the study were as summarized in Table 5. Nausea and vomiting was seen significantly higher in the pentazocine group (36%) when compared to butorphanol (20%) and nalbuphine (8%) groups ($p<0.05$ each). There were no reports of hypotension or respiratory depression in any of the study groups (Table 5).

DISCUSSION

Our understanding of the physiology of pain and pain pathways has increased considerably and more effective pain-relieving medications have become available in the last decade. Despite this, post-operative pain continues to be under-treated.[7,8] Opioids are the mainstay of post-operative pain management. They may be underused in post-operative situations due to many reasons, including lack of knowledge about effective dose ranges and duration of action, fear of adverse effects and concerns regarding their addiction potential. The currently available opioid agonist-antagonist agents have demonstrated excellent analgesic effectiveness in the management of post-operative pain. We aimed to compare the analgesic efficacy and safety of three opioid agonist-antagonists' pentazocine, butorphanol and nalbuphine in alleviating post-operative pain.

Our study used a randomized double blind design. The profile of patients and the nature of surgery can have an influence on the subjective response to pain. Our study selected female patients undergoing lower abdominal surgery and the patient demographic profiles, ASA grades and the nature of surgeries were well matched between the three groups. Also, the pre-anesthetic medications and anesthetic techniques were almost similar in all patients. We used equinalgesic doses of these three agents in the study. The VAS scores at the time of administration of study analgesic were very similar in all the three groups, which implied that the degree of pain at baseline was also well matched.

Time to onset of analgesic action is an important parameter in the assessment of clinical efficacy of analgesics in the management of post-operative pain.[9] In this study, nalbuphine and butorphanol demonstrated significantly faster onset of action than pentazocine.

In the comparative study in post-surgical pain by North et al, significant analgesic activity was noted by 10 minutes of administration in the both the butorphanol (2 and 4 mg) and pentazocine (60mg) groups.[10] In the study by Lokeswari and colleagues in post-operative pain management, IM nalbuphine demonstrated significantly faster onset of action (14.66 minutes) than butorphanol (34.76 minutes) for post-operative pain management.[11] Dobkin and coworkers compared three doses of butorphanol (1, 2, or 4mg) and two doses of pentazocine (30 or 60 mg) given intramuscularly for post-operative pain. In their study appreciable pain relief was seen by 30 minutes in all the dose groups.[12]

Rapid onset of analgesic activity can be advantageous by providing quicker relief of post-operative pain, thereby increasing patient comfort. The faster onset of activity with nalbuphine and butorphanol over pentazocine in our study may indicate the benefit of these agents in post-operative pain management setting.

The duration of analgesic action seen noted with the three analgesics in our study was consistent with their pharmacokinetic properties.[13] Nalbuphine and butorphanol showed significantly longer duration of analgesia when compared to pentazocine. Nalbuphine showed prolonged analgesic efficacy approximating four hours on average and ranging up to six hours. Butorphanol also had a long duration of analgesia

approximating 3.3 hours. Pentazocine had the shortest duration of analgesia of approximately 3 hours among the three agents.

In the study by Lokeswari, the mean duration of analgesia with nalbuphine was 6.05 hours (range 4-12 hours) and with butorphanol it was 5.2 hours (range 4-8 hours).[11] Dobkin AB study reported that in their study with all doses butorphanol (1, 2, or 4 mg) and pentazocine (30 or 60 mg), satisfactory analgesia was seen for 4 hours.[12] North et al reported that the analgesic effect of butorphanol was slightly longer than that of pentazocine.[10] Longer duration of analgesic effect observed with nalbuphine can be a preferable attribute in the post-operative period by prolonging the period of comfort and avoiding additional medications, which can increase the possibility of adverse effects.

In our study, there were no significant hemodynamic disturbances noted in any of the study groups. Previous studies have also demonstrated that these three agents have good hemodynamic stability.[10-12]

Drowsiness is a known major adverse effect seen with opioid agonist-antagonist agents. Although, we noted that numerically higher proportion of patients with conscious analgesia in the nalbuphine group at one hour after administration, the three groups was not statistically different in terms of sedation. There were no incidents of respiratory depression in any of the groups. Pruritus, which is a common side effect seen with opioids mediated through agonism at mu receptors was not seen with any of the agents in this study.

Nausea and vomiting, which are known adverse effects of opioids were noted at lower levels (8%) in the nalbuphine group compared to 20% in butorphanol group and 36% in the pentazocine group. Nalbuphine has demonstrated the advantage of lower nausea and vomiting rates compared to other opioids in previous studies.[14-16] In the study by Lokeswari, the incidence of both nausea (9.9% vs. 33.3%) and vomiting (6.7% vs. 26.7%) were significantly lower in the nalbuphine group compared to the butorphanol group.[11] Post-operative nausea and vomiting is known to increase patient discomfort, delay discharge and increase the hospitalization costs.[17,18] The low incidence of this side effect with nalbuphine can be a particular advantage in post-operative pain relief settings.

In summary, the findings of our study indicate that nalbuphine and butorphanol appears to be more effective and safer analgesics when compared to equianalgesic dose of pentazoine for post-operative pain management in gynecologic lower abdominal surgery. Nalbuphine when compared to other opioid agonist-antagonists in this study can be a useful agent for post –operative pain relief because of its quicker onset, longer duration of action and lower incidence of adverse effects such as sedation, nausea and vomiting.

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