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# A Comparison of Morphine and Nalbuphine for Intraoperative and Postoperative Analgesia

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## Abstract

### Introduction:

Short acting narcotics are not available in Pakistan and the supply of drugs like morphine and pethidine is short and erratic; therefore there is a need for investigating acceptable alternatives for analgesia, to be used for balanced anaesthesia.

### Objective:

We studied the agonist-antagonist narcotic nalbuphine compared to morphine, for intra and postoperative pain relief in total abdominal hysterectomies.

### Methods:

In a randomised double blind trial, fifty ASA I and II patients in two groups of twenty five each were given equianalgesic doses of morphine and nalbuphine. Hemodynamic stability, intraoperative analgesia, recovery profiles, incidence of side effects and need for postoperative supplements were compared using standard anaesthesia technique for induction, maintenance and reversal. Postoperative analgesia profile was studied by the need for supplements in twenty four hours using the unidimensional verbal category scale.

### Results:

We found that patients in the morphine group showed a rise of mean blood pressure and heart rate to 20% above the baseline in response to intubation whereas in the nalbuphine group it remained within 20% of baseline. Twelve out of twenty five patients in the morphine group and four out of twenty five patients in the nalbuphine group needed intraoperative supplements. Recovery profiles were similar in the two groups; postoperative nausea and vomiting and need for postoperative supplements was significantly less in the nalbuphine group.

### Conclusion:

We conclude that nalbuphine provides better haemodynamic stability and better analgesia, recovery profile and postoperative pain relief compared to morphine in patients undergoing total abdominal hysterectomy (JPMA 53:391;2003).

## Introduction

Short acting narcotics like fentanyl, sufentanyl and alfentanyl are not available in Pakistan, and supply of pure narcotics like pethidine and morphine to hospitals is erratic. Use of agonist-antagonist analgesics for both intraoperative and postoperative analgesia is an acceptable alternative.<sup>1,2</sup> These drugs have the advantage of easy availability and low abuse potential.<sup>3,4</sup>

The relevant data is available for Caucasian population<sup>5,6</sup> but there is a need for randomized controlled trials of these drugs on the local population.

This study was designed to compare the analgesic efficacy, cardiovascular effects, recovery profile and intra and postoperative complications of the agonist-antagonist narcotic, nalbuphine, with equianalgesic doses of the pure agonist morphine in the intra and immediate postoperative period.

### **Patients and Methods**

The study was approved by the ethical committee of the Aga Khan University. Fifty ASA I and II female patients, aged 20 to 60 years undergoing total abdominal hysterectomy were studied. Informed consent was taken and patients were randomly allocated to two groups A and B, of twenty five patients each. Randomization was by the envelope method. Patients of physical status ASA III and IV, with known allergy to opioids and anticipated difficult intubation were excluded from the study.

All patients were premedicated with 7.5 mgs of oral midazolam an hour before surgery. Baseline recordings of heart rate and blood pressure were taken in the operating room; Group A received Morphine 0.1 mg/kg and group B received Nalbuphine 0.2 mg/kg. Each drug was diluted in a total volume of 10 ml and the syringes were labelled "study drug" to make the study blind. The calculated dose of the study drug was given by an anaesthetist unconnected with the study, five minutes before induction.

Heart rate and blood pressure was taken five minutes after drug administration. After preoxygenation with 100% oxygen anaesthesia was induced with 4 mgs / kg of thiopentone and muscle relaxation achieved with 0.1 mg/kg of pancuronium. Patients were ventilated to normocapnia with nitrous oxide and oxygen in a ratio of 66:33%. The trachea was intubated three minutes later with size 8.0 red rubber orotracheal tube.

Halothane 0.5 to 1% was added to nitrous oxide during maintenance of anaesthesia.

Supplements of pancuronium were given as required. Supplemental doses of 2.5 ml of "study drug" were given if two out of four of the following signs of insufficient analgesia were present: lacrimation, sweating, heart rate more than 20% above the baseline and blood pressure more than 20% above the baseline. At least 10 minutes were allowed between injection of study drug and skin incision. The number of supplemental injections of study drug given were noted for each patient.

Heart rate, electro-cardiogram, end-tidal carbon dioxide tension and arterial oxygen saturation were monitored using the Datex Ohmeda monitoring system. Non-invasive blood pressure was monitored continuously using Dinamap at five minute intervals throughout the procedure.

Halothane was discontinued 5 to 10 minutes before reversal. Nitrous oxide was discontinued just before reversal. Reversal of muscle relaxant was achieved with atropine 0.02 mg/kg and neostigmine 0.05 mg/kg. Extubation was done when pre-laid criteria for extubation were fulfilled. The mean time between reversal and opening eyes on command and ability to tell name was noted. Patients were also specifically asked about the presence of any pain at the operative site. All patients were kept in the recovery for one hour. The requirement of analgesic and occurrence of any side effects like nausea, vomiting or respiratory depression (respiratory rate less than 10/minute), sweating, or hypertension were noted.

The postoperative analgesic requirements were assessed using the verbal category scale. This scale classifies pain based on its perception by the patient as mild, discomforting, distressing, horrible or excruciating.<sup>7</sup> Supplement was given if pain was described as discomforting or distressing by the patient.

Statistical analysis was done by entering and analysing the variables on Microsoft Excel. The mean change in systolic, diastolic and mean blood pressure, heart rate, and recovery profile was compared between groups by using the unpaired student-t test. The intragroup analysis was done by using the paired t-test. Chi square test was used for discrete data; p-value of less than 0.05 was considered significant for all the variables.

### **Results**

Demographic data (Table 1)

No significant difference was observed between the two groups.

Haemodynamic variables

a) Systolic Blood Pressure (SBP) changes (Figure 1).

**Morphine group**

The mean baseline blood pressure in the morphine group was  $137 \pm 14$  mm of Hg. The blood pressure decreased to a maximum of 11% compared to baseline following induction. A maximum rise of blood pressure to 13% of baseline was observed at one minute following intubation, which returned to baseline by 3 minutes, and remained 7% below baseline until after skin incision.

**Nalbuphine group**

The mean baseline blood pressure in this group was  $142 \pm 17$  mm of Hg. It decreased to a maximum of 15% compared to baseline following induction. The maximum rise in blood pressure after intubation was 9% compared to baseline, which returned to baseline at 3 minutes and remained below the baseline following the skin incision.

**Inter-group comparison**

The SBP difference recorded at three and four minutes following intubation show a significant difference between the two groups ( $p$ -value  $< 0.05$ ), with lower values recorded in the nalbuphine group.

b) Diastolic Blood Pressure (DBP) changes (Figure 2).

**Morphine group**

The baseline mean diastolic blood pressure in the morphine group was  $84.4 \pm 8.0$  mm of Hg. The change from baseline was minimal following induction. The maximum rise of DBP was 27% above the baseline at one minute following tracheal intubation, which returned to baseline at five minutes post-intubation. Following the skin incision, the readings were 4 to 5% above baseline for 3 minutes.

**Nalbuphine group**

The baseline mean diastolic blood pressure in this group was  $85.6 \pm 6$  mm of Hg. The change from baseline was minimal following induction. The maximum rise in DBP was 21% above baseline at one minute post-intubation; it returned to baseline by three minutes post-intubation. The change from baseline following the skin incision was minimal.

**Intergroup comparison**

Statistically significant difference in DBP was recorded at three and four minutes post-intubation with lower values in the nalbuphine group.

c) Mean Blood Pressure (MBP) changes (Figure 3).

**Morphine group**

The baseline mean blood pressure in this group was  $99.8 \pm 9$  mm of Hg. A maximum rise in MBP to 21% of the baseline was seen 1 minute after intubation, which returned to baseline by five minutes post-intubation. Following the skin incision no significant change was seen.

**Nalbuphine group**

The baseline mean blood pressure was  $104.6 \pm 10$  mm of Hg in this group. Five minutes after the study drug it was 6% below the baseline. Following induction it was 12% below the baseline. A maximum rise to 14% above the baseline was recorded at one minute following intubation, which returned to baseline by two minutes post-intubation. There was no significant change following the skin incision.

**Intergroup comparison**

Statistically the MBP values at 3 and 4 minutes post-intubation showed a significant difference ( $p$ -value  $< 0.01$ ), with lower values in the nalbuphine group.

d) Heart Rate (HR) changes (Figure 4).

**Morphine group**

The baseline mean in this group was  $90.6 \pm 15$  beats /minutes. No significant change was seen 5 minutes after study drug and following induction. Following intubation it remained 20 - 22% above the baseline at 1, 2, 3, 4 and 5 minutes. Three minutes after the skin incision it was 10% above the baseline.

**Nalbuphine group**

The baseline mean in this group was  $95.5 \pm 15$  beats /minute. The change was minimal at 1, 2 and 3 minutes following induction. The maximum rise was 13% above the baseline 1 minute after intubation, returning to baseline by five minutes after intubation. The change from baseline

following the skin incision was insignificant.

Intergroup comparison

A statistically significant difference between the two groups was observed at 3, 4 and 5 minutes post-intubation and 1, 2 and 3 minutes post skin incision, with lower values in the nalbuphine group.

Recovery profile (Table 2)

Duration of anaesthesia was similar between the two groups. No difference was observed in the mean time between reversal of muscle relaxation and opening eyes on command. A statistically significant difference was observed in the mean time between reversal and patient's ability to tell name, with lesser time taken in the morphine group (11.3 mins.) compared to nalbuphine group (16.2 mins).

Analgesic efficacy (Table 3)

Four (16%) patients in the nalbuphine group, and twelve (48%) patients in the morphine group required intraoperative analgesic supplements. Pain at reversal was present in five (20%) patients in the morphine group but in none of the patients in the nalbuphine group.

Postoperative supplements were required by fifteen (60%) patients in the morphine group and seven (28%) patients in the nalbuphine group. The duration between last intraoperative and first postoperative supplement was also significantly greater i.e., 4.1 (SDM) hours in the morphine group, and 5.8 (SDM) hours in the nalbuphine group ( $p$ -value  $<0.05$ ).

Side Effects (Table 4)

1. Nausea: Five (20%) patients in the morphine group, and 1 (4%) patient in the nalbuphine group had nausea in the recovery room. This difference was not statistically significant ( $p$ -value  $>0.05$ ).
2. Vomiting: Five (20%) patients in the morphine group and 1 (4%) patient in the nalbuphine group had vomiting in the recovery room. This difference was not statistically significant ( $p$ -value  $>0.05$ ).
3. Other Side Effects: None of the patients in either group had any other side effect such as respiratory rate less than 10/minute, hypertension, hypotension, sweating or arrhythmias.

## Discussion

Pure opioid agonists like morphine and pethidine carry the risk of dose related respiratory and cardiovascular depression<sup>8,9</sup> nausea, vomiting<sup>10</sup> and addiction potential.<sup>11</sup> The supply of these drugs to hospitals in Pakistan is also erratic. Nalbuphine is an agonist - antagonist opioid analgesic with cardiovascular stability<sup>12,13</sup> and lesser potential for respiratory depression.<sup>14,15</sup> It is a non-controlled drug and is easily available in the country. It has been used as an intra and postoperative analgesic in the Caucasian population<sup>5,6</sup> but there is lack of data regarding its use in the local population in Pakistan.

In the present study we have compared the analgesic efficacy, haemodynamic stability, recovery profile and side effects of nalbuphine 0.2 mgs/kg with morphine 0.1 mg/kg, in patients undergoing total abdominal hysterectomy. The dose selected was on the basis of ED 50 of nalbuphine established in rats as 1.2 mg/kg compared to 0.98mg/kg of morphine indicating its potency to be 0.7 to 0.8 times that of morphine.<sup>3</sup> Higher dose requirements were needed in clinical anaesthesia in humans.<sup>1,5</sup> Doses varied between 1.5 to 2 mg/kg. The clinically recommended ceiling is 20 mg / 70 kg.<sup>15</sup>

The 0.2 mg/kg dose of nalbuphine proved to be hemodynamically more stable compared to 0.1mg/kg of morphine. The haemodynamic response to intubation differed significantly in the two groups, with the response being lower in the nalbuphine group. The rise in systolic, diastolic and mean blood pressures and heart rate remained within 20% of the baseline in both groups.

The haemodynamic response to skin incision was also lower in the nalbuphine group.

Haemodynamic parameters remained within 20% of the baseline in both groups; the highest response was 15% above baseline in the morphine group and 9% in the nalbuphine group.

These observations are similar to previously reported studies in the Caucasian population.

Fahmy found no significant change in arterial blood pressure, cardiac output, heart rate or right atrial pressure from baseline values in patients undergoing bilateral hip replacement under general anaesthesia, who received nalbuphine for analgesia.<sup>1</sup> Zsigmund reported similar results in balanced anaesthesia for neurosurgery<sup>17</sup> and the same results were seen in balanced anaesthesia with nalbuphine in general surgery by Magruder.<sup>5</sup> Even in high doses of 3.0 mg/kg

used as part of balanced anaesthesia in cardiac surgery, nalbuphine was shown to have less circulatory depressant effects than morphine.<sup>12</sup> This is a significant advantage in surgical patients with ischemic heart disease and hypertension, and neurosurgical procedures where blood pressure swings contribute to morbidity.

The analgesic efficacy was assessed by the need for intraoperative supplements, presence of pain at reversal, duration between last intraoperative dose and first postoperative dose, and the number of patients in each group who needed supplements in the recovery room. The results showed a statistically significant difference between the two groups. Intraoperative supplements were required by 16% patients in the nalbuphine group compared to 48% patients in the morphine group.

None of the patients in the nalbuphine group had pain at reversal compared to five in the morphine group. The time between the last intraoperative and first postoperative was significantly longer in the nalbuphine group, i.e., 5.8 hours whereas in the morphine group this was 4 hours. These results are similar to other studies of nalbuphine in balanced anaesthesia, in doses of 0.2 to 0.5mg/kg; Fahmy and Magruder both reported nalbuphine analgesia as highly satisfactory in the intraoperative period, with no pain on waking up and greater time interval in the demand for postoperative analgesia, in orthopaedic and general surgery.<sup>1,5</sup>

Fifteen patients in the morphine group compared to seven patients in the nalbuphine group required analgesic supplements in the recovery room. A significant difference was observed between the two groups with a higher number of patients in the morphine group requiring supplements in the immediate postoperative period than in the nalbuphine group.

Statistically significant difference was recorded at all time intervals except opening eyes to command, with the nalbuphine intervals being marginally longer than those of morphine. This is in contrast to other balanced anaesthesia studies which report rapid emergence and orientation with nalbuphine.<sup>5,6</sup> Our results show that the recovery time is slightly longer with nalbuphine compared to morphine; however in our clinical settings we do not consider it a serious disadvantage.

The side effects studied were respiratory depression, (respiratory rate of less than 10/minute on arrival in the recovery room), nausea and vomiting, sweating, hypertension, hypotension, arrhythmias, headache, dizziness, excessive drowsiness or skin rashes. None of the patients in either group developed any of these adverse effects. With nalbuphine this was consistent with ceiling effect of partial agonists on respiratory depression, as observed in other studies.<sup>2,5</sup> This is a significant advantage in recovery room areas, especially in a developing country like Pakistan where availability of equipment and trained health care personnel is limited.

Lesser number of patients complained of nausea and vomiting in the nalbuphine group, which is consistent with lesser inhibition of gastrointestinal motility by partial agonists. This has been observed in other studies.<sup>18</sup> We consider this a significant advantage for use of nalbuphine in ear, nose and throat, gynaecological, biliary and day case surgery; as it relates to patient comfort as well as cost effectiveness and value based practice emphasized in today's cost conscious health care system.

## **Conclusion**

We conclude that nalbuphine in a dose of 0.2 mg/kg provided better analgesia and greater haemodynamic stability, as a component of balanced anaesthesia in lower abdominal surgery, with a lower incidence of nausea and vomiting in the postoperative period compared to morphine 0.1 mg/kg. Although the recovery profile for nalbuphine was found to be slightly longer than for morphine, we did not consider it a serious disadvantage. The duration of analgesia with nalbuphine was significantly longer, reducing the need for supplements in the immediate postoperative period. This will result in cost saving and will have financial implications in a developing country.

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