Nalbuphine versus Morphine as Part of Intravenous Anesthesia Post Cardiac Surgery

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Abstract

Objectives: The analgesic properties of nalbuphine mixed agonist antagonist opioid, in the postoperative period are well known. Our prospective study aims to compare nalbuphine and morphine as intravenous anesthetics together with propofol infusion, in the early postoperative period, following cardiac surgery.

Methods: 40 patients with ASA I-III scheduled for elective primary isolated coronary artery bypass grafting were included. Nalbuphine group (20 patients) received nalbuphine administrated by intravenous continuous infusion once arrived in cardiac intensive care unit. Morphine group (20 patients) received morphine by intravenous continuous infusion once arrived in cardiac intensive care unit. Changes in hemodynamic variables greater than 20% above or below the baseline, VAS and sedation score, receiving additional doses of analgesia and incidence of complications are all analysed in all patients.

Results: Both groups are comparable in their baseline demographic and surgical characteristics. Blood pressure remained within 20% of baseline in the nalbuphine group whereas, rise in mean blood pressure and heart rate more than 20% of base line occurred in the morphine group. 30% of patients in the nalbuphine group required additional doses of analgesia, compared to 70% of the morphine group. VAS and sedation score were significantly better in the nalbuphine group than the morphine group. Incidence of vomiting and pruritis were significantly higher in the morphine group compared to the nalbuphine group.

Conclusion: We concluded that Nalbuphine provided better hemodynamic stability, effective postoperative pain relief, with fewer complications, compared to morphine in patients post cardiac surgery.

Keywords: Nalbuphine; Morphine; Pain; Sedation; Pressure; Cardiac

Introduction

Nalbuphine is a semi-synthetic opioid having strong analgesic effects because of its agonist effects on K opioid receptors in the central nervous system (CNS). It has been shown that nalbuphine is either equipotent with morphine or has near equipotence [1]. Inspite of its agonist effects on the µ opioid receptors, its administration is accompanied by sedation, urinary retention and disphoria[9]. Haemodynamic adverse effects in patients especially with cardiac diseases are shown to be minor. Nalbuphine compared with morphine, shows lower incidence of vomiting as well. Its half-life is to some extent short, about 3 to 6 hours [2]. Its onset of action ranged from 5-10 min after its intravenous administration [3], and its duration of action is 3-6 hours [4]. Morphine is an active metabolite of morphine 6 glucoronide that causes respiratory depression, sedation as well as analgesia. Its onset of action is about 30-60 min after its intravenous administration and its duration of action is about 4-6 hours [5].

The aim of this prospective study was to compare nalbuphine and morphine administered through intravenous infusion, in the postoperative period following cardiac surgery.

Methods

This prospective study was approved by institutional ethical committee of Ain Shams University and was performed in Ain Shams University hospital. Written informed consent was obtained from every patient.

We included 40 ASA I-III physical status patients aged from 45-60 years old undergoing a scheduled elective cardiac surgery with expected moderate to severe postoperative pain.

The patients did not present with morbid obesity, physical or mental retardation, or oesophageal reflux, allergy to these drugs, and had not received opioids at least one month before the surgical procedure. The patients were randomly allocated to two groups Nalbuphine group (20 patients) to receive nalbuphine (bufigen 10 mg/ml; laboratoriospi sa, mexico DF, mexico) in an initial dose of 10 mg administered over 30 sec followed by IV continuous infusion (5 mg/hr) started up on arrival at the ICU and Morphine group (20 patients) to receive initial dose (1-3 mg) followed by IV infusion at a rate of 2 mg/hr once arrived at the ICU. They are maintained for the next 24 hours postoperatively. Randomization was established by the allocation concealment.

Bolus doses of either nalbuphine or morphine were prepared in 20 ml of NaCl 0.9% sterile solution and administered during a 10 min period. The infusion of nalbuphine and morphine were prepared daily in a NaCl 0.9% solution that was administered by means of on automatically-controlled infusion pump. Adminstration of NaCl 0.9% was independent of the fluids administered to the patients as part of the post- surgical treatment.

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Demographic characteristics (age, weight and height) were compared between groups.

Evaluation of the patient’s pain intensity using visual analogue score scale. A VAS consisting of 10 cm line drawn horizontally on paper with right angle stops placed at both ends where zero corresponding to no pain and 10 is the worst imaginable pain, was explained to the patients twice before the surgery and once they recovered their alert state [6].

We didn’t observe any difficulty in explaining the scale and patients did not express any problem in understanding the scale itself nor in scoring their pain.

For the purposes of this study “adequate pain relief” was defined as achieving a pain score of less than four that is mild to no pain during 24 hours period. This designation was included on the VAS scale was stated to the patients.

The first assessment of postoperative analgesia was performed using VAS 2 hours postoperatively and thereafter at 6,16,24 hours post operatively.

The level of sedation was evaluated using Ramsay sedation scale. [7]. It was a scale to be defined for sedated patients and was designed as a test of reusability. The RSS scores sedation at six different levels, where 1 means that patient is alert while 6 means patients exhibits no response pre and post operatively. The level of sedation was assessed according to whether the patient was awake and alert, sleep and easy to arouse, difficult to arouse, responded by shaking or didn’t respond [8].

The mean diastolic and systolic blood pressure was monitored throughout 24 hours interval.

We recorded the rate of incidence of complications as vomiting and pruritis within 24 hour period. Vomiting was defined as forcible expulsion of gastric contents through oral route, the number of each episode was noted, in case of persistence of symptoms, 10 mg IV metoclopramide was used.

Pruritis was defined by its presence or absence and was treated with reassurance or diphenhydramine 25 mg on demand if reassurance was ineffective.

We recorded the number of patients receiving additional doses of opioids. If the pain intensity score was ≥4 cm, the infusion rate was increased where 1 means that patient is alert while 6 means patients exhibits no response pre and post operatively. The level of sedation was assessed according to whether the patient was awake and alert, sleep and easy to arouse, difficult to arouse, responded by shaking or didn’t respond [8].

The minimal sample size was less than or equal 40 By type I error 5% and type II error 10% with power of test 90% by Med Calc 7.1.

Demographic characteristics were compared between groups using t test where T test value is an indicator of T test and X^2 value is an indicator of Chi-Square test, and a p-value≤0.05 was considered statistically significant.

Demographic characteristics were shown as mean ± SD.

VAS and sedation scores were compared between groups using Mann-Whitney, best and p-value≤0.05 was considered statistically significant.

VAS and sedation scores were compared within the group according to the time using Friedman test. p-value<0.05 was considered the statistically significant.

Systolic and diastolic blood pressure changes were compared between the study groups using T test and p-value≤0.05 was considered statistically significant.

Results

All patients completed the study in their corresponding group and were evaluated as planned by the protocol.

Demographic characteristics were similar between the nalbuphine and morphine groups. No significant difference (p>0.10) was observed between groups in any of the parameters (Table 1).

As regards to the additional boluses of narcotics, in the morphine group Significantly more patients required rescue bolus doses of opioids within the first post-surgical 24 hours (70%:30%) (Table 2).

Significantly more patients experiencing vomiting in the morphine group. Vomiting in the morphine group was associated with dose increments (Table 2).

Significantly more patients experienced pruritis in morphine group compared with nalbuphine group (Table 2).

Visual analogue scale score was similar between the 2 groups in the first 2 hours post-operative.

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Visual analogue scale score was similar between the 2 groups in the first 2 hours post-operative.

Visual analogues scores were significantly lower in the nalbuphine group compared with the morphine group at 6, 16, 24 hours post-operative (Table 3) (Figure 1).

### Table 1: Demographic data.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Nalbuphine Group</th>
<th>Morphine Group</th>
<th>T/X^2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Range</td>
<td>45.790-65.840</td>
<td>46.360-61.820</td>
<td>0.490 (t)</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>54.508 ± 6.503</td>
<td>53.687 ± 3.718</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>Range</td>
<td>17.130-29.240</td>
<td>17.700-28.440</td>
<td>-0.742 (t)</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>23.176 ± 3.501</td>
<td>23.899 ± 2.591</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>13 (65%)</td>
<td>11 (55%)</td>
<td>0.417 (x^2)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>7 (35%)</td>
<td>9 (45%)</td>
<td></td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>Range</td>
<td>60.060-81.070</td>
<td>60.920-83.830</td>
<td>-0.138 (t)</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>71.097 ± 5.546</td>
<td>71.322 ± 4.759</td>
<td></td>
</tr>
<tr>
<td>Ht (cm)</td>
<td>Range</td>
<td>156.840-196.310</td>
<td>160.540-185.510</td>
<td>1.059 (t)</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>176.149 ± 10.224</td>
<td>173.206 ± 7.070</td>
<td></td>
</tr>
</tbody>
</table>

BMI: Body Mass Index; Wt.: Weight; HT: Height.

T-test value is an indicator of T test and X^2 test value is an indicator of Chi-Square test.
Significantly difference between the 2 groups regarding Ramsay sedation score (p<0.001) (Table 4) (Figure 2). Mean systolic blood pressure values were insignificant between the 2 study groups preoperatively. Systolic blood pressure values were significantly lower in nalbuphine group compared with morphine group (p<0.001) postoperatively (Table 5).

Insignificant difference in the mean diastolic blood pressure between the 2 groups preoperatively.

Significantly lower mean diastolic blood pressure in nalbuphine group compared with morphine group (p<0.001) post operatively (Table 6).

Discussion
There are many ways for postoperative pain management ranging from regional blocks with local anesthetics to systemic administration of synthetic opioids. Postoperative pain control is now crucial and takes the attention of many clinicians. Take into mind that a proper balance between analgesic efficacy and safety is really a challenge. Morphine is a potent analgesic, but it causes higher rate of vomiting and respiratory depression [9]. This study was done to compare the analgesic efficacy of nalbuphine (a kappa agonist) compared with morphine (a predominantly Mu agonist) following cardiac surgery. Nalbuphine 10 mg IV loading dose followed by IV infusion rate of 5 mg/hr may probably resulting in a better control of postoperative pain compared with IV bolus dose of morphine 1-3 mg followed by IV infusion rate of 2 mg/hr without any significant adverse effects. The chosen dose of Nalbuphine proved to be more hemodynamically stable. A study performed on rats, using 1.2 mg/kg nalbuphine compared with 0.98 mg/kg of morphine showing that nalbuphine potency is 0.7 times of morphine [10]. So we found that higher dose requirements of nalbuphine needed for analgesia in humans. This may result from the fact that the analgesic action of nalbuphine is not pharmacokinetically equivalent. The most clinically recommended bolus dose of nalbuphine 10 mg IV loading dose followed by IV infusion rate of 5 mg/hr may probably resulting in a better control of postoperative pain.[10].

**Table 3:** Visual analogue score scale in the postoperative period in both groups.

<table>
<thead>
<tr>
<th>VAS</th>
<th>Nalbuphine Group</th>
<th>Morphine Group</th>
<th>Mean rank</th>
<th>Mann-Whitney Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>Range 7-9</td>
<td>Range 7-9</td>
<td>18.200</td>
<td>22.800</td>
</tr>
<tr>
<td></td>
<td>Median (IQR) 8 (1)</td>
<td>8 (0.75)</td>
<td>12.350</td>
<td>28.650</td>
</tr>
<tr>
<td>T6</td>
<td>Range 5-7</td>
<td>Range 6-8</td>
<td>5 (1)</td>
<td>14.325</td>
</tr>
<tr>
<td></td>
<td>Median (IQR) 5 (1)</td>
<td>7.5 (2)</td>
<td>11.275</td>
<td>29.725</td>
</tr>
<tr>
<td>T16</td>
<td>Range 2-5</td>
<td>Range 3-6</td>
<td>4.5 (1.75)</td>
<td>5.5 (1)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR) 2 (1)</td>
<td>5 (1.75)</td>
<td>10.417</td>
<td>18.200</td>
</tr>
<tr>
<td>T24</td>
<td>Range 1-3</td>
<td>Range 2-6</td>
<td>58.306</td>
<td>51.133</td>
</tr>
<tr>
<td></td>
<td>Median (IQR) 2 (1)</td>
<td>5 (1.75)</td>
<td>8 (1)</td>
<td>10 (50%)</td>
</tr>
</tbody>
</table>

T2: 2 hours postoperatively; T6: 6 hours postoperatively; T16: 16 hours postoperatively; T24: 24 hours postoperatively

**Table 2:** The need extra dose of analgesia and the side effect profile.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Nalbuphine gp</th>
<th>Morphine gp</th>
<th>X²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for extra dose</td>
<td>5 (25%)</td>
<td>14 (70%)</td>
<td>8.120</td>
<td>0.004</td>
</tr>
<tr>
<td>Pruritis</td>
<td>1 (5%)</td>
<td>5 (25%)</td>
<td>3.383</td>
<td>0.066</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (15%)</td>
<td>10 (50%)</td>
<td>5.584</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Need extra dose: the number of patients needed additional doses of opioids.
T-test value is an indicator of T test and X² test value is an indicator of Chi-Square test.
results of our study. Wandless I showed that nalbuphine is a better alternative to morphine in control of post orchiopexy surgical pain with greater safety and convenience [17]. Minai FN et al. showed that nalbuphine resulted in better hemodynamic stability and analgesic effects compared with morphine in patients undergoing total abdominal hysterectomy [18]. Kruszynsk et al. concluded that in a single-blinded trial of laparoscopic versus open appendectomy in children: effects on postoperative analgesia. Anesthesiology 84: 801-806.


