

## 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 administered 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]. In spite of its agonist effects on the  $\mu^2$  opioid receptors, its administration is accompanied by sedation, urinary retention and dysphoria [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 glucuronide 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 (buprenorphine 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 an automatically-controlled infusion pump. Administration of NaCl 0.9% was independent of the fluids administered to the patients as part of the post-surgical treatment.

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**Received** August 04, 2014; **Accepted** November 05, 2014; **Published** November 14, 2014

**Citation:** Shokri H, Ali I (2014) Nalbuphine versus Morphine as Part of Intravenous Anesthesia Post Cardiac Surgery. J Anesth Clin Res 5: 463. doi:10.4172/2155-6148.1000463

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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  $\geq 4$  cm, the infusion rate was increased to 1 ml/hr and remained for this rate level for 24 hrs unless sedation occurred. Thirty minutes after the infusion rate was increased patients were requested to evaluate the pain intensity. If it remained at  $\geq 4$  cm, IV bolus of either nalbuphine 5 mg or morphine 2 mg over 2 minutes was administered if required a bolus dose was repeated 2 hours later.

## Statistical Analysis

All analysis was performed with spss version 19.

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/x<sup>2</sup> test where T test value is an indicator of T test and X<sup>2</sup> test value is an indicator of Chi-Square test, and a p-value $\leq 0.05$  was considered statistically significant.

Demographic characteristics were shown as mean  $\pm$  SD.

VAS and sedation scores were compared between groups using Mann-Whitney, best and p-value $\leq 0.05$  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  $\leq 0.05$  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.

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).

		Groups		Test	
		Nalbuphine Group	Morphine Group	t/X <sup>2</sup>	P-value
Age	Range	45.790-65.840	46.360-61.820	0.490 (t)	0.627
	Mean $\pm$ SD	54.508 $\pm$ 6.503	53.687 $\pm$ 3.718		
BMI (kg/m <sup>2</sup> )	Range	17.130-29.240	17.700-28.440	-0.742 (t)	0.462
	Mean $\pm$ SD	23.176 $\pm$ 3.501	23.899 $\pm$ 2.591		
Sex	Female	13 (65%)	11 (55%)	0.417 (x <sup>2</sup> )	0.519
	Male	7 (35%)	9 (45%)		
Wt (kg)	Range	60.060-81.070	60.920-83.830	-0.138 (t)	0.891
	Mean $\pm$ SD	71.097 $\pm$ 5.546	71.322 $\pm$ 4.759		
Ht (cm)	Range	156.840-196.310	160.540-185.510	1.059 (t)	0.296
	Mean $\pm$ SD	176.149 $\pm$ 10.224	173.206 $\pm$ 7.070		

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

T- test value is an indicator of T test and X2 test value is an indicator of Chi-Square test

**Table 1:** Demographic data.

	Groups		Chi-square Test	
	Nalpuhine gp	Morphine gp	X <sup>2</sup>	P-value
Need for extra dose	5 (25%)	14 (70%)	8.120	0.004
Pruritis	1 (5%)	5 (25%)	3.383	0.066
Vomiting	3 (15%)	10 (50%)	5.584	0.018

Need extra dose: the number of patients needed additional doses of opioids.

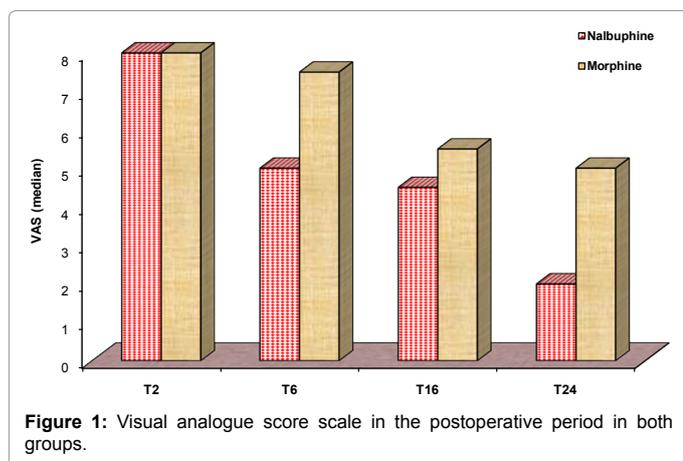
T-test value is an indicator of T test and X<sup>2</sup> test value is an indicator of Chi-Square test

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

VAS		Groups		Mean rank		Mann-Whitney Test	
		Nalpuhine Group	Morphine Group	Group I	Group II	Z	P-value
T2	Range	7-9	7-9	18.200	22.800	-1.355	0.175
	Median (IQR)	8 (1)	8 (0.75)				
T6	Range	5-7	6-8	12.350	28.650	-4.635	<0.001
	Median (IQR)	5 (1)	7.5 (2)				
T16	Range	2-5	3-6	14.325	26.675	-3.518	<0.001
	Median (IQR)	4.5 (1.75)	5.5 (1)				
T24	Range	1-3	2-6	11.275	29.725	-5.091	<0.001
	Median (IQR)	2 (1)	5 (1.75)				
Friedman Test	X <sup>2</sup>	58.306	51.133				
	P-value	<0.001	<0.001				

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

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



**Figure 1:** Visual analogue score scale in the postoperative period in both groups.

Significantly difference between the 2 groups regarding Ramsay sedation score ( $p \leq 0.001$ ) (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 expected, depending on its complex pharmacodynamic profile [1,11]. Previous studies showing that analgesic effect of both drugs are equivalent. The most clinically recommended bolus dose of nalbuphine was 10 mg/70 kg [12]. Lake et al. showed that nalbuphine caused less respiratory depression compared with morphine even when it was used in higher doses (3 mg/kg) in cardiac surgery so we were not worried from increasing the dose [13]. In previous trials, morphine bolus dose ranged from 0.5 mg to 2.5 mg, the most commonly used bolus dose was 1 mg. The maximum hourly dose of morphine was 6 mg/h so we chose the most frequently used dose which proved to be effective and safe particularly in cardiac patients [14]. Nalbuphine is a partial agonist while morphine is a pure agonist [15]. Nalbuphine has dominantly spinal components while morphine has spinal and supraspinal components [15]. Morphine results in pruritus however nalbuphine does not show this side effect [15]. In our study, regarding postoperative vomiting, morphine caused significantly this side effect, on the contrary nalbuphine, this finding disagreed with another study by Shiv et al. who showed no statistically significant difference between the study drugs regarding vomiting, they also reported that sedation scores were similar in both groups; this is in contrast to the

Sedation score		Mean rank		Mann-Whitney Test			
		Nalbuphine Group	Morphine Group	Group I	Group II	Z	P-value
T2	Range	1-2.	2-3.	12.000	29.000	-4.907	<0.001
	Median (IQR)	1 (1)	2.5 (1)				
T6	Range	1-4.	2-5.	13.825	27.175	-3.763	<0.001
	Median (IQR)	2 (1)	4 (1.75)				
T16	Range	2-5.	2-4.	25.300	15.700	-2.728	0.006
	Median (IQR)	4 (2)	3 (1)				
T24	Range	1-2.	2-3.	14.100	26.900	-3.950	<0.001
	Median (IQR)	2 (1)	2 (1)				
Friedman Test		X <sup>2</sup>	52.119				
		P-value	<0.001				

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

Table 4: Ramsay sedation score of patients of both groups in the post-operative period.

SBP		Nalbuphine Group	Morphine Group	T-test	
Pre	Mean ± SD	115.150 ± 4.626	115.000 ± 3.129	0.120	0.905
Post	Mean ± SD	117.900 ± 3.370	125.550 ± 4.947	-5.716	<0.001
Difference	Mean ± SD	-2.750 ± 5.210	-10.550 ± 5.206		
Paired t-test	t	-2.361	-9.063		
	P-value	0.029	<0.001		

Table 5: Systolic blood pressure in pre and post-operative periods in both groups.

SBP		Nalbuphine Group	Morphine Group	T-test	
Pre	Mean ± SD	69.200 ± 2.840	69.000 ± 1.835	0.265	0.793
Post	Mean ± SD	71.450 ± 2.704	87.450 ± 4.925	-12.734	<0.001
Difference	Mean ± SD	-2.250 ± 4.038	-18.450 ± 5.125		
Paired t-test	t	-2.492	-16.101		
	P-value	0.022	<0.001		

Table 6: Mean diastolic blood pressure in pre and postoperative periods in both groups.

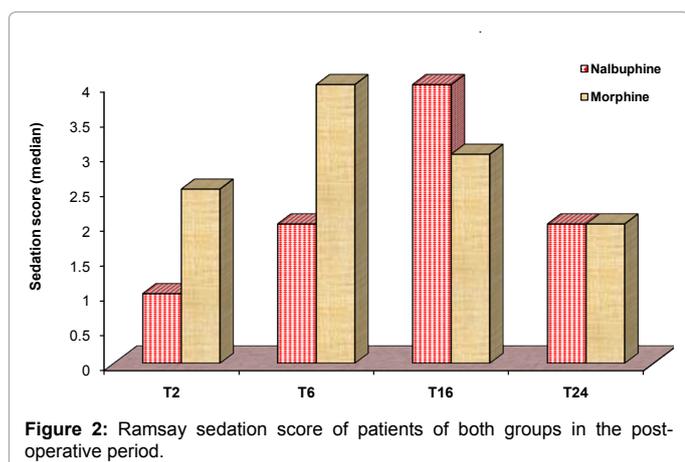


Figure 2: Ramsay sedation score of patients of both groups in the post-operative period.

results of our study. Wandless IJ showed that nalbuphine is a better alternative to morphine in control of post orchiopey 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]. Kruszynski et al. concluded that in a proper dose, nalbuphine is a better analgesic alternative to morphine regarding analgesic efficacy and duration of pharmacological action in gynecological surgical procedures [19]. The major limitation of our

study was the lack of blinding because of the small sample size which opens the channel for criticism of observer bias.

## Conclusion

We concluded that nalbuphine showed better postoperative pain control and more hemodynamic stability as well without any significant complications in relation to morphine in patients undergoing cardiac surgery.

## Acknowledgement

This work was supported by both, Cardiothoracic Surgery department and Anesthesiology department, Ain Shams university, Cairo, Egypt.

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