

## Original Article

# Impact of preoperative intramuscular injection of nalbuphine on postoperative pain in elderly patients received arthroplasty

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**Abstract:** Objective: To investigate the effect of preoperative nalbuphine intramuscular injection on postoperative pain in elderly patients who received total hip replacement or hemiarthroplasty. Methods: A total of 60 elderly patients who received total hip or hemi-hip arthroplasty during October 2016 to April 2017 in Gansu Provincial Hospital were included in the study. They were randomized into the control group and the nalbuphine group. The nalbuphine group received intramuscular nalbuphine injection at 8:00 pm in the day before the day for operation, while the control group was given placebo. We observed and recorded the visual analogue score (VAS) at 30 minutes (T1), 2 hours (T2), 6 hours (T3) and 12 hours (T4) after surgery and meanwhile recorded quality of life and postoperative adverse reaction at day 1 after admission, one day before operation, 24 hours after operation and 48 hours after operation. Results: Compared with the control group, the nalbuphine group had lower visual analogue scores and higher quality of life scores at each time observed. No significant adverse reaction happened in both of the two groups. Conclusion: Nalbuphine pretreatment is useful for postoperative pain management of elder patients who receive hip arthroplasty.

**Keywords:** Nalbuphine, elderly patients, analgesia, hip arthroplasty

## Introduction

China faces a serious of issues arising from population aging [1]. With the population aging, the morbidity of femoral neck fracture in old age increases as well. Selective total hip replacement or hemiarthroplasty has been a common operation to improve quality of life for elderly patients with femoral neck fractures [2]. However, because aged people present functional declines in major organs, concomitant diseases, poor tolerability to the hemodynamic fluctuations, there are risks and special requirements in the anesthesia and surgery for elderly patients [3]. Patients tend to suffer from anxiety and poor quality of sleep before orthopedic surgery, which could increase the uncertainties during the anesthesia and surgery, as well as the morbidity of postoperative delirium [4]. Preemptive analgesia is a method that gives patient anesthesia before noxious stimuli gen-

erate, which is helpful to relieve postoperative pain and reduce the use of postoperative anesthetic [5].

Nalbuphine hydrochloride is a mixed opioid receptor agonist-antagonist (an antagonist at  $\mu$  receptor agonists and an agonist at  $\kappa$  receptor), which is widely used in western countries for analgesia [6]. Nalbuphine has a similar effect of analgesia as morphine, but has less inhibiting effect on respiratory function; it has a ceiling effect [7]. Research has shown that the effective anesthesia time of nalbuphine could last for 5 hours, and it had no inhibiting effect on cardiovascular system, which was suitable for elderly patients [8].

The purpose of this study was to observe security and effectiveness of nalbuphine hydrochloride in analgesia of elderly patients who received selective arthroplasty.

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## Materials and methods

### General information

A total of 60 elderly patients (over 65 years old) who received total hip replacement or hemiarthroplasty during October 2016 to April 2017 were included in this study. Inclusive criteria: Patients who were over the age of 65 and received unilateral total hip replacement; patients who were sound in hepatorenal, coagulation and neurological functions. Exclusive criteria: Patients who were addicted to analgesic or anesthetic; patients with serious complications such as cardiovascular diseases, hepatic and renal diseases or hematological diseases; patients with cognitive disorder. All patients showed sound baseline characteristics before surgery; they all received epidural anesthesia. All of the patients signed informed consent. The research was approved by Ethics Committee of Gansu Provincial Hospital. The patients included were randomized into the control group (Con) and the nalbuphine group (Nal), with each group having 30 patients.

### Methods

The patients were taught to fill in the visual analogue score (VAS) and the questionnaire of sleep quality and analgesic effect. The Nal group was given 1 mL (10 mg) of nalbuphine hydrochloride (SFDA approval number 12120H207, produced by Yichang Humanwell Pharmaceutical co., Ltd.) by intramuscular injection while the Con group didn't receive preoperative analgesic. Both groups received standardized postoperative analgesia. Their blood pressure and heart rate were monitored.

### Outcome measurements

We observed and recorded the VAS of the patients in 30 minutes (T1), 2 hours (T2), 6 hours (T3) and 12 hours (T4) after surgery. As for VAS, a score of 1-3 represents the mild pain which patients can tolerate and do not impact patients' sleep and activities; 4-6 represents moderate pain that has some impacts on patients' sleep and activities; 7-9 scores represent severe pain that has a serious impact on patients' sleep and activities.

Meanwhile, we also recorded the sleep quality and analgesic effect using QoR-15 question-

naire at day 1 after admission, one day before surgery, 24 hours after surgery and 48 hours after surgery, respectively. QoR-15 questionnaire is a simple self-rating life quality scale containing 10 items: respiratory, appetite, feeling (whether relax or not), communication with family and friends, medical support, work or family activities, a sense of comfort and self-controlled, overall feeling of health status, etc. Each item can be scored from 0 to 10. Lower score equals to worse general condition. Assessment of satisfaction degree of analgesia contains mild pain, severe pain, nausea vomiting, etc. Each item can be scored from 0 to 10. Lower score indicates more severe pain. The assessment of emotion mainly contains mental status, appetite, attention and the levels of anxiety of patients. Each item can be scored from 0 to 5. Lower score equals to a more unstable emotion [7]. The assessment of sleep quality mainly contains the time of falling asleep, the total sleeping time, the times of waking up, and the feeling after waking up. Each item can be scored from 0 to 5. Lower score equals to a poorer sleep quality [8]. At the meantime, the incidence of adverse reactions within 3 days after surgery was recorded, including sedative effect, nausea, vomiting, vertigo, etc.

### Statistical analysis

SPSS software was used to analyze the data. Data of VAS, sleep quality assessment were expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm sd$ ). Variance analysis of repeated measures was used to compare the data of multiple time points, while the independent sample t test was used to compare the data of single time points. Enumeration data are expressed as frequency with the  $\chi^2$  test.  $P < 0.05$  means the difference is statistically significant.

## Results

### Baseline characteristics

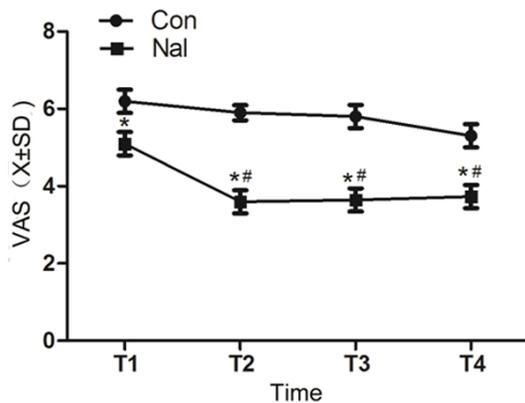
There were no significant differences in age, sex, body mass index (BMI), weight, surgery duration and bleeding volume between the two groups ( $P > 0.05$ ). After surgery, 3 patients suffered from moderate or severe pain in the Nal group, while 7 in the Con group. The incidence of severe pain in the Nal group was significantly

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**Table 1.** Compare of general clinic information of the two groups (mean  $\pm$  standard deviation)

Groups	Con group (n=30)	Nal group (n=30)	t value	P value
Age (year)	62.36 $\pm$ 5.49	64.25 $\pm$ 6.21	2.439	0.084
Sex (M/F)	19/11	22/8	2.392	0.087
BMI (kg/m <sup>2</sup> )	23.35 $\pm$ 2.18	25.63 $\pm$ 2.39	2.726	0.062
Weight (kg)	57.29 $\pm$ 3.27	59.61 $\pm$ 4.62	2.583	0.075
Operation Duration (min)	127.38 $\pm$ 18.74	134.63 $\pm$ 21.74	3.164	0.059
Blood loss volume (mL)	186.26 $\pm$ 17.46	192.19 $\pm$ 21.27	2.629	0.069
Patients of moderate or severe pain (case)	3	7	4.752	0.031

Note: Con group: control group; Nal group: nalbuphine group; M: male; F: female; BMI: body mass index.



**Figure 1.** Effect of nalbuphine on patients' postoperative pain self-evaluation score. VAS: visual analogue score; Con: control group; Nal: nalbuphine group; T1: 30 minutes after operation; T2: 2 hours after operation; T3: 6 hours after operation; T4: 12 hours after operation. \*P<0.05, compared at the same time point with the control group. #P<0.05, compared at the time point of T1.

lower than that in the Con group (P<0.05). See **Table 1**.

### Analgesic effect

Compared with the Con group, the Nal group had significantly lower scores of VAS at 30 minutes, 2, 6, and 12 hours after surgery respectively (all P<0.05). See **Figure 1**.

### Adverse reactions

The package inserts of nalbuphine indicated that the most common adverse reaction of this drug was sedative effect, followed by nausea and vomiting. Under the dosage regimen in the study, patients were stable in their blood pressure and heart rates. No case of respiratory depression was observed. There was 1 case of nausea and vomiting and 1 case of vertigo in

the Nal group, while there was 1 case of vertigo in the Con group. There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05).

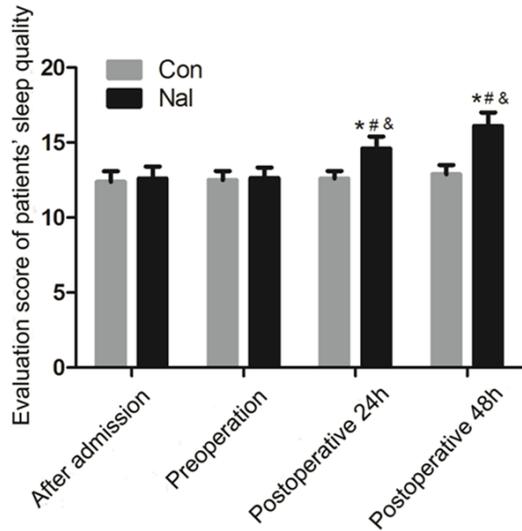
### Sleep quality and satisfaction degree of analgesia

The results of the self-evaluation of the patients showed that Nal group had higher sleep quality, more relaxed emotion and confidence in postoperative recovery than the Con group. The score of each item significantly increased in the Nal group. Quality of life in the Nal group improved, which would contribute to the effect of the treatment. The results also showed that in the Nal group after preoperative analgesia and in the 24 hours after surgery, the pain was under control, the nervous emotion was relieved and patients reported higher satisfaction degree of analgesia. See **Figures 2-4**.

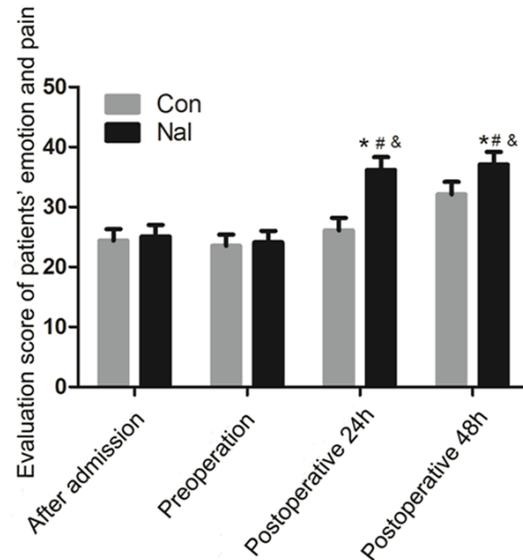
### Discussion

Nalbuphine hydrochloride is a common opioid analgesic regulating pain-related  $\mu$  receptor and  $\kappa$  receptor, and is widely used in surgeries [9]. The study of Bidlack et al. showed that nalbuphine and morphine had strong anesthetic effects. Nevertheless, nalbuphine could reduce the incidence of pruritus, respiratory depression, etc. [10]. Preemptive analgesia could decrease noxious stimuli during the surgery to the central nervous system by giving analgesic before operation. The mechanism was that the peripheral nerve block could reduce the incoming signals of pain-sensitive nerves and could also decrease the sensibility of the central nerves, resulting in analgesia [11]. Konopitski et al. found that patients who received knee surgery felt much less postoperative pain after preemptive analgesia [12]. Our study focused

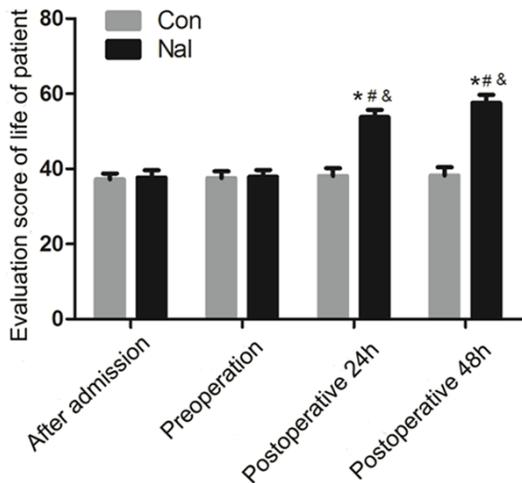
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**Figure 2.** Effect of nalbuphine on patients' self-evaluation score of sleep quality. Con: control group; Nal: nalbuphine group. \* $P < 0.05$ , compared with the control group at the same time point. # $P < 0.05$ , compared with the admission time of the same group. & $P < 0.05$ , compared with the preoperative time of the same group.



**Figure 4.** Effect of nalbuphine on patients' self-evaluation score of emotion and pain. Con: control group; Nal: nalbuphine group. \* $P < 0.05$ , compared with the control group at the same time points; # $P < 0.05$ , compared with the admission time of the same group; & $P < 0.05$ , compared with the preoperative time of the same group.



**Figure 3.** Effect of nalbuphine on patients' self-evaluation score of life quality. Con: control group; Nal: nalbuphine group. \* $P < 0.05$ , compared with the control group at the same time points; # $P < 0.05$ , compared with the admission time of the same group; & $P < 0.05$ , compared with the preoperative time of the same group.

on the effect of preoperative analgesia of nalbuphine hydrochloride to elderly patients suffered from femoral neck fracture. The results indicated that patients presented lower VAS scores at 2 and 6 hours after surgery, respec-

tively. The analgesic effect diminished 12 hours after surgery. The analgesic effect of the Nal group was much better than that of the control group, suggesting that nalbuphine hydrochloride significantly relieved the patients' postoperative pain, which is consistent with the results of previous studies [13].

A study found that adverse reactions like mild respiratory depression, nausea, vomiting and vertigo happened in some of the patients who were given 10 mg of nalbuphine through intravenous injection. However, this was not statistically different from those in the control group. Larger dose of analgesic through intravenous injection was required to maintain the analgesic effect, resulting in an incidence of adverse reactions as high as 12.6% [14]. Our study found that intramuscular injection of nalbuphine took effect fast. There was no case of respiratory depression, 1 case of nausea and vomiting and 1 case of vertigo identified in the nalbuphine group. The incidence of adverse reactions was 6.7%, indicating that intramuscular injection was associated with significantly decreased incidence of adverse reaction.

Elderly patients, especially patients over 70 years old, are usually complicated by diseases

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such as hypertension, diabetes mellitus or hyperlipemia. The fracture and postural restriction could lead to pain and negative emotions like fear and anxiety, seriously affecting patients' quality of life [15]. With a certain sedative effect, nalbuphine allowed patients to go to sleep easier and to have higher sleep quality [16]. High-quality sleep is helpful to pacify emotions, reduce secretion of gastric acid caused by anxiety and relieve the stress responses such as rising blood pressure, which is beneficial for the procedure of anesthesia and surgery [17, 18].

Non-steroidal anti-inflammatory drugs are widely used in clinics to control mild pain. However, these drugs also have limitations such as insufficient analgesic effect, hepatic and renal function impairments, increased risk of gastrointestinal hemorrhage and delayed healing of the fracture [19]. Therefore, the opioid receptor agonist-antagonist could be a better choice with higher security and better analgesic effects. Some studies indicate that spinal  $\kappa$  receptor also plays a role in anti-inflammation, with a certain analgesic effect. Moreover, it was more unlikely to cause addiction and respiratory depression by inhibiting  $\mu$  receptors. The major adverse reaction of exciting central  $\kappa$  receptor was sedative effect, but it could be helpful to reduce anxiety of the hospitalized patients [20-22]. Our study has proven that nalbuphine was good in analgesia. But the study didn't discuss the combined use of nalbuphine and other analgesics. More studies are warranted to explore the potential of nalbuphine hydrochloride.

In conclusion, nalbuphine hydrochloride has proved a certain effect of analgesia, only with a few mild adverse reactions. It could be a new choice of pain management during the perioperative period.

### Disclosure of conflict of interest

None.

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