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# The Effect of an Intravenous Bolus of Ultra-Low-Dose Naloxone on Intraoperative Sedation, Post Operative Pain Intensity and Morphine Consumption in Cesarean Section Patients under Spinal Anesthesia

Mustafa Sadeghi, Ali Movafegh and Behrang Nouralishahi
Department of Anesthesiology and Critical Care, Dr. Ali Shariati Hospital,
Tehran University of Medical Sciences, Tehran, Iran

**Abstract:** Different drugs from various pharmacological classes have been used to enhance postoperative opioid analgesia and reduce adverse effects. Animal studies have demonstrated that co-administration of an ultra-low-dose opioid antagonist with an opioid agonist may result in enhanced analgesia. Investigation of this effect in humans has been limited and produced inconsistent findings. In this study, 60 patients were randomized into 2 groups to receive either 2 mL saline (control group) or received IV dose of 100 ng $kg^{-1}$ naloxone (diluted with normal saline to 2 mL) (naloxone group) after to the administration of spinal anesthesia (15 mg 0.5% hyperbaric bupivacaine). After administration of IV medication (saline or naloxone), sedation were scored with the Richmond Agitation-Sedation Scale at times 0, 5, 20, 30 min, respectivily. Following the surgery, patients were asked to score the pain (using 10-cm Visual Analog Scale (VAS) at the arrival in the ward and 2, 4, 8, 12 and 24 h, respectivily after surgery. The presence of Postoperative Nausea and Vomiting (PONV) and pruritus were recorded. All enrolled patients received post-operative intravenous analgesia delivered through a PCA pump. The demographic characteristics of patients, ASA physical status class, duration of surgery, basal VAS and basal sedation score were similar in the 2 groups. Total dose of morphine (38.3±10.7 mg in C group and 23.5±7.1 mg in N group, independent t test<0.001), the VAS pain score at time intervals (Mann-Whitney u test, $p<0.001$) and the intraoperative sedation score (Mann-Whitney u test, $p<0.001$) were significantly lower in the naloxone group. There were no significant differences in incidence of PONV and pruritus in groups.

**Key words:** Ultra-low dose, naloxone, analgesia, sedation

## INTRODUCTION

Despite advances in the management of postoperative pain, many patients still suffer from postoperative pain, due to difficulties in balancing a reliable, prolonged and effective pain regimen with acceptable side-effects (Pogatzki-Zahn and Zahn, 2007). Opioid analgesics remain the most effective means of relieving pain for a wide variety of conditions (Bijur *et al*., 2006); however, they may cause adverse effects such as nausea, vomiting, pruritus, urinary retention and respiratory depression (Movafegh *et al*., 2006; Yu *et al*., 2002; Booth *et al*., 2000). As the analgesia and the side effects of opioids are dose-dependent, a multimodal approach may enhance analgesia while minimizing the side effects (Movafegh *et al*., 2006).

Animal studies have demonstrated that co-administration of an ultra-low-dose opioid antagonist with an opioid agonist may result in enhanced analgesia. Investigation of this effect in humans has been limited and produced inconsistent findings (Gan *et al*., 1997).

The purpose of the current study was to determine whether administration of IV bolus of ultra-low-dose naloxone prior to the administration of spinal bupivacaine anesthesia in cesarean section patients would induce intraoperative sedation, enhance analgesia and minimize Postoperative Nausea and Vomiting (PONV) compared with a control group.

## MATERIALS AND METHODS

The protocol was approved by the Institutional Ethics Committee and informed written consent was obtained from the patients. Sixty patients, 20-40 years, classified as ASA physical status I and II who were undergoing cesarean section, were enrolled in this randomized, double-blinded and placebo-controlled study. Patients who received opioids within the past 7 days or antiemetic therapy within 48 h of surgery; those with a history of motion sickness, PONV or addiction; those with any contraindication to spinal anesthesia or naloxone administration were excluded from the study.

**Corresponding Author:** Ali Movafegh, Department of Anesthesiology and Critical Care, Dr Ali Shariati Hospital, North Karegar Street, Tehran 1411713135, Iran

At the preoperative visit, a trained investigator explained to the patient the study plan, the different scales used in the study and how to use the patient control analgesia (PCA) system. All drugs were prepared by an anesthetist who was not involved in the anesthesia administration nor in patient observation, thus, both the anesthesiologist and the patients were blinded to the group assignment. Patients were randomly assigned into 2 groups of either control (Group C, n = 30) or naloxone (Group N, n = 30) using a computer generated randomization list.

On arrival in the operating room, all patients were routinely monitored with an Electrocardiogram (ECG), noninvasive blood pressure and pulse oximetry.

An 18-gauge cannula was inserted and lactated ringer solution 7 mL $kg^{-1}$ was administered. Intrathecal anesthesia was instituted in the left lateral position. Using an aseptic technique, a 25-gauge sprotte needle was inserted via a midline approach into the L3-4 or L4-5 interspaces. Both groups received 15 mg 0.5% hyperbaric bupivacaine and then the patients were immediately placed in supine position. The patients in Group C received 2 mL saline intravenously and those in Group N received IV dose of 100 ng $kg^{-1}$ naloxone (diluted with normal saline to 2 mL) after to the administration of spinal anesthesia. The level of sensory blockade was assessed by level of the touch sensation prior to surgical incision (T4-6 was considered adequate). Supplemental oxygen 6 L $min^{-1}$(35%) was administered via a vent mask during and after surgery. Arterial blood pressure was monitored every 3 min for the first 21 min following the intrathecal drug administration and then every 5 min thereafter. Reduction in mean arterial pressure more than 15% below pre-anesthetic baseline was treated by incremental doses of ephedrine 5 mg IV, decline of heart rate to less than 50 bpm was treated by IV atropine (0.5 mg). Nausea and vomiting were treated with metoclopromide (10 mg). The treatment was repeated if necessary.

After administration of IV medication (saline or naloxone), sedation score were measured with the Richmond Agitation-Sedation Scale (4 = combative, 3 = very agitated, 2 = agitated, 1 = restless, 0 = alert and calm, -1 = drowsy, -2 = light sedation, -3 = moderate sedation, -4 = deep sedation, -5 = unarousable) (Sessler *et al*., 2002) at times 0, 5, 20 and 30 min.

The severity of post operative pain was measured and recorded using 10-cm Visual Analog Scale (VAS), where 0 = no pain and 10 = the worst possible pain. Patients were asked to score the pain during coughing or movement at arrival in the ward and 2, 4, 8, 12 and 24 h, respectivily after surgery.

The incidence of nausea, vomiting and pruritus was evaluated by a "yes" or "no" survey. All evaluations were performed and recorded at arrival in the ward and 1, 2, 4, 8, 12 and 24 h, respectivily after surgery.

All enrolled patients received post-operative intravenous analgesia delivered through a PCA pump (Accumate 1000). The PCA pump was loaded with morphine hydrochloride 1 mg $mL^{-1}$ diluted in 0.9% NaCl and was programmed to deliver, on request, a 1-mg morphine bolus with a lock-out period of 6 min between two consecutive boluses.

Based on a pilot study of 10 patients (5 in each group), we determined that a sample size of 25 in each group would be sufficient to detect a difference of 3 scores in the mean of VAS score estimating a standard deviation of 3, a power of 95% and a significance level of 5% and this number has been increased to 30 per group, to allow for a predicted drop-out from treatment of around 10%. Statistical analysis was performed using SPSS package (SPSS Inc., Chicago, IL, USA), version 13.

The distribution of age, height, weight, surgery time, morphine consumption and VAS for pain was checked by the Kolmogorov-Smirnov test. Except VAS for pain, they followed a normal distribution. Age, weight, height, surgery time and morphine consumption were compared between 2 groups by independent sample t-test. The sedation scores was an ordinal scale measurement. To compare the sedation scores and VAS for pain between 2 groups in each time of measurement, Mann-Whitney u test were used. To compare the sedation scores and VAS for pain within group against time, the Friedman test was used. The sex, ASA physical status class, PONV and pruritus were compared with chi-square test. Two tailed $p<0.05$ was taken as significant.

## RESULTS

Three patients (Two from group C and one from group N) were excluded from the study, because of failure of administration of intrathecal anesthesia and for whom general anesthesia was used.

Patient characteristics, perioperative fluid administration, level of sensory blockade and the duration of surgery were similar in the 2 groups (Table 1).

Patients who received an ultra-low dose of naloxone showed increased level of sedation at 5, 20 and 30 min compared to control group(Mann-Whitney u test, $p<0.001$) (Table 2). Furthermore, in patients who received naloxone, there was a significant change in sedation levels over time compared with basal value (Friedman test, $p<0.001$).

Table 1: Patient characteristics

| | Control group (n = 28) | Naloxone group (n = 29) |
|---|---|---|
| Age (Year) * | 28.8±6.2 | 26.3±5.6 |
| Weight (kg) * | 83.8±11.2 | 83.0±9.9 |
| Height (cm)* | 160.6±8 | 160.4±6.4 |
| Post-op fluid administration (L) * | 2.9±0.29 | 2.8±0.25 |
| Surgery time (minutes) * | 38.0±9.5 | 39.1±11.0 |
| Sensory blockade level (T6/T8) | 22/6 | 20/9 |
| ASA Class (I/II) | 21/7 | 25/4 |

*Values are expressed as mean±SD, **There are no significant differences among the groups

Table 2: Sedation in groups

| | Control group (n = 28) | Naloxone group [b] (n = 29) |
|---|---|---|
| Immediately after medication** | 0.5(0-2) | 1(0-2) |
| 5 minutes after [a] medication | 0(-2-2) | -2(-3-1) |
| 20 minutes after [c] medication | 0(-1-1) | 0(-2-1) |
| 30 minutes after [a] medication | 0(-2-1) | 0(-2-1) |

*Values are expressed as median (range), **There are no significant differences among the groups, (a). p<0.001(Mann-Whitney u test), (b). p<0.001(Friedman test), (c). p = 0.002(Mann-Whitney u test)

Table 3: VAS pain score at 6-hours intervals, total dose of morphine, nausea and vomiting, and pruritus numbers

| | Control group[b] (n = 28) | Naloxone group[b] (n = 29) |
|---|---|---|
| VAS pain score at 6-hours intervals | | |
| 0 h** | 2.5(0-6) | 2.0(1-8) |
| 1 h[c] | 6.0(2-10) | 5.0(1-10) |
| 2 h[a] | 8.0(4-9) | 4.0(2-8) |
| 4 h[a] | 7.0(2-9) | 3.0(1-9) |
| 8 h[a] | 6.5(3-9) | 3.0(1-9) |
| 12 h[a] | 6.0(2-9) | 2.0(1-7) |
| 24 h[a] | 3.5(1-10) | 1.0(0-6) |
| Total dose of morphine (mg)[d] | 38.3±10.7 | 23.5±7.1 |
| 24-h Nausea and Vomiting number (percent) ** | 4(14.2%) | 6(21.4%) |
| Pruritus number (percent) ** | 3(10.7%) | 1(3.4%) |

*Values are expressed as median (range), **There are no significant differences among the groups, (a). p<0.001(Mann-Whitney u test), (b). p<0.001(Friedman test), (c). p = 0.002(Mann-Whitney u test), (d). p<0.001 (independent t test)

After 2 h, there was significant difference in the mean of VAS for pain measured over time between the 2 groups (Mann-Whitney u test, Between-Subjects effects, p<0.001). The changes in VAS for pain over time was significant in each group (Friedman test, p<0.001) (Table 3).

There was significant differences in the mean of the 24 h morphine consumption (38.3±10.7 mg in C group and 23.5±7.1 mg in N group, independent t-test<0.001) between the 2 groups (Table 3).

There were no significant differences in the incidence of PONV and pruritus in groups (Table 3).

## DISCUSSION

The current study demonstrates that the intravenous administration of 100 ng $kg^{-1}$ naloxone prior to spinal bupivacaine anesthesia produces mild intraoperative sedation, reduces the intensity of postoperative pain and the opioid consumption. The incidence of PONV and pruritus are similar.

Activation of opioid receptors has generally been considered to produce inhibitory effects on neuronal activity. However, recent evidence indicates that opioids can elicit excitatory as well as inhibitory modulation of the action potentials of sensory neurons. Ultra-low-doses of opioid antagonists could selectively block the excitatory effects of opioids (Crain and Shen, 2000). There is evidence to suggest that naloxone has a dose-dependent pain response in both animal and human species. In a rat model, small doses of naloxone produce paradoxical analgesia, whereas larger doses result in hyperalgesia (Levine and Gordon, 1986; Woolf, 1980; Levine *et al*., 1979). Clinically, ultra-low-dose naloxone has demonstrated the enhancement of morphine analgesia in an acute intra-operative setting (Wang *et al*., 2005). Why would a small-dose naloxone paradoxically enhance analgesia? Opioids have traditionally been thought to produce their analgesic effects via agonist binding to Gi/o-receptor–coupled complexes. Gi/o-coupled receptors inhibit electrical firing of neurons through the opening of inwardly rectifying $K^+$_ channels and the closing of voltage-gated $Ca^{++}$_channels (Nestler *et al*., 2001). Crain and Shen (2000) have proposed that opioids also bind at remarkably small doses (pico or nano-Molar concentrations) to Gs-coupled receptors. Gs-coupled receptors activate adenylyl cyclase, are coupled to an excitatory second messenger system (protein kinase A), increase $Ca^{++}$_ion channel conductance, close inwardly rectifying $K^+$_ channels. Opioid binding to Gs protein–coupled receptors may therefore be responsible for the hyperalgesia occasionally reported with opioid administration and with some opioid-induced side effects, such as pruritus and nausea and vomiting. They also hypothesized that small doses of opioid antagonists may decrease opioid-induced side effects and improve pain control by inhibiting only the excitatory G protein receptor complexes and leaving the inhibitory complexed receptors available for pain control (Crain and Shen, 2000).

Although, we used small doses of naloxone successfully for postoperative pain relief, some studies have not corroborated our results (Bijur *et al*., 2006; Sartain *et al*., 2003; Cepeda *et al*., 2002). A possible reason for divergent findings is that the dose of opioid antagonists used in the human studies may be too high and is thus antagonizing both the inhibitory and excitatory modes. Second, some of these studies didn't assess postoperative pain and they studied different populations such as emergency patients (Bijur *et al*., 2006).

Most of the studies in which the antagonist was effective, had chosen naloxone infusion (Gan *et al*., 1997; Maxwell *et al*., 2005). Perhaps, short duration of action of naloxone could explain these observations. However, in our study, IV bolus ultra-low dose naloxone successfully reduced post operative pain intensity and morphine consumption. We used naloxone in patients received spinal and not general anesthesia. May be it could explain the reason of this difference. Naloxone in low doses has been shown to release endorphins, or perhaps displaces endorphins from receptor sites (Gan *et al*., 1997). So, may be this phenomena explains naloxone induced intraoperative sedation in our patients.

Some previous studies demonstrated that small dose of naloxone could reduce opioids side-effects, but the incidence of PONV and pruritus in our study were similar in groups. Perhaps our sample size was simply too small to observe any difference in the development of PONV and pruritus.

## CONCLUSION

In conclusion, we demonstrate that intravenous administration of 100 ng $kg^{-1}$ naloxone prior to spinal bupivacaine anesthesia is a valuable treatment as it induces mild intraoperative sedation and reduces postoperative pain intensity and morphine consumption.

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