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The Effect of Epidural Morphine-Bupivacaine Combined with a Low Dose of Naloxone on Respiratory Function and Analgesia in Patients with Chronic Low-Back Pain

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Abstract

Context: Hypoventilation and apnea after epidural morphine is a serious concern after surgery and an issue in chronic pain. A low dose of naloxone added to morphine can prevent this complication.

Objective: To determine that the low dose of naloxone added to epidural morphine analgesic could change the effect of this opioid in chronic low back pain. In addition, we evaluate its effect on respiratory function and patient satisfaction.

Patients: Twenty-seven adults suffering from chronic low back pain (LBP) who were candidates for epidural injection treatment.

Intervention: This was a randomized double-blind, uniform crossover, controlled clinical trial. The patients were treated with mixture of morphine-bupivacaine and mixture of morphine-bupivacaine-naloxone.

Main outcome measure: The primary goals were to evaluate pain intensity and respiratory function after epidural injection of morphine or morphine combined with naloxone.

Secondary end-points were the incidence and the side effects (pruritus, nausea, vomiting, and urinary retention) of neuraxial injection of morphine or morphine combined with naloxone for 14 days after each epidural injection.

Results: There was no significant difference between morphine and morphine combined with naloxone on mean peripheral capillary oxygen saturation (SpO_2m), the lowest peripheral capillary oxygen saturation (SpO_2), and the respiratory disturbance index (RDI). Morphine combined with naloxone seemed to decrease pain more than morphine alone, but the result was not significant (p=0.2116). In the group that received morphine and naloxone, pain decreased sooner by half from baseline pain (at day 2 *versus* at day 6) than the other group. Vomiting, pruritus, and urinary retention were seen with no significant difference in both groups.

Conclusion: We conclude that epidural administration of naloxone can preserve the analgesic effect of morphine in treatment of chronic LBP. Naloxone does not have any effects on respiratory function. It reduces itching, nausea, and pruritus after epidural injection of morphine. We cannot be certain whether this is the ideal dose or whether any changes in the doses might produce fewer side effects without interfering with analgesia.

Keywords: Hypoventilation; Morphine; Surgery; Chronic pain

Introduction

Over 70% of people in industrialized countries will experience Lower Back Pain (LBP) at some point in their lives. Lower Back Pain is the second most common cause of missed workdays in the United States [1-4]. Due to the diverse underlying aetiologies and pathologies that cause LBP and variation in symptom presentation, different methods, medications, and procedures are used for treatment. In chronic LBP, opioids are one of the most commonly used medications [5-8]. Tolerance to analgesic is the major challenge faced in long-term opioid use, which requires increasing doses that lead to more adverse effects. Based on studies, it has been shown that low doses of opioid antagonists could prevent opioid tolerance [9,10]. This clinical trial aimed to evaluate the effects of adding a low dose of naloxone to epidural morphine injections not only on pain analgesia, but also on respiratory functions and the other adverse effects of epidural morphine.

Method

Study setting

Subjects diagnosed with chronic low back pain lasting for more than three months were identified and referred to the pain clinic by their primary care physician. The study took place between August 2004 and October 2005.

Study design

The Research Ethics Committee of Centre Hospitalier de L'Université de Montréal (CHUM) approved the study. Subjects who agreed to participate provided written informed consent. A randomized, double-blind, uniform crossover, controlled clinical trial was conducted. We

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used two mixture treatments: treatment A - an epidural injection of 1 mg morphine plus 10 mg bupivacaine, and treatment B - an epidural injection of 1 mg morphine plus 10 mg bupivacaine plus 0.08 mg of naloxone. Twenty-seven patients were randomly assigned to one of two groups (group A|B and group B|A). Treatment group A|B subjects first received treatment A then crossed over, after a washout period of 15 days, to receive treatment B, whereas group B|A subjects started by receiving treatment B, and after a washout period of fifteen days, followed by treatment A (Figure 1).

Inclusion criteria

Patients older than 18 years of age with chronic LBP, lasting more than three months, with or without leg or radicular pain were included.

Exclusion criteria

Patients with clinically significant cardiovascular diseases (recent cardiovascular events, severe hypertension), severe chronic obstructive pulmonary disease (forced expiratory volume of 1s (FEV1) <50% of predicted values), history of psychiatric disease, history of allergy to any of the medications in the study, anticoagulant therapy, pregnancy, recent (<2 months) epidural injection, and history of substance abuse were excluded from the study. Inability to read or understand the consent form, language barrier, no telephone access, chronic pain other than chronic LBP, and technical difficulties performing the epidural procedure were also criteria for exclusion from the study.

Epidural injection

A pain clinic specialist performed the procedure. The procedure was performed with 17-gauge Tuohy needle, and the loss-of-resistance technique with an air-filled syringe was used to identify the epidural space. A 21-gauge epidural catheter was introduced through the Tuohy needle and directed upwards 3 to 5 cm into the epidural space. After removing the Tuohy needle, the study solution was injected through the catheter.

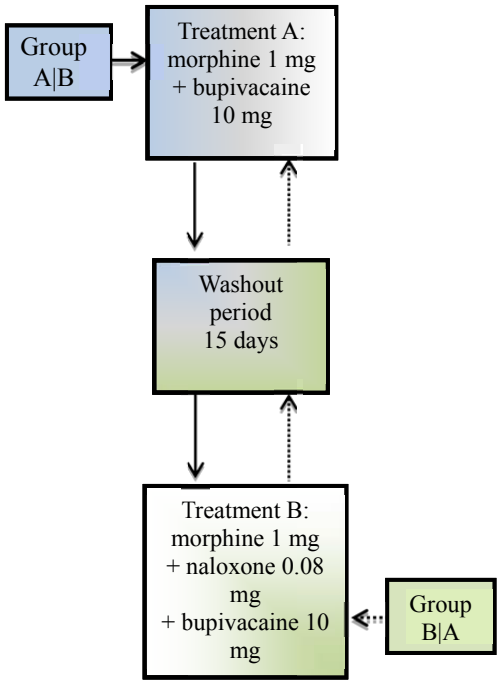

Figure 1: Study design.

The patients were monitored for at least 30 minutes after each procedure. During these periods, pain level, hemodynamic parameters, and side effects were measured.

Remmers sleep recorder

The Remmers Sleep Recorder is an ambulatory sleep recorder designed by SagaTech (Calgary, Canada). The device has been clinically validated for unattended sleep studies in a home environment [11,12].

The Remmers Sleep Recorder samples the oxygen saturation (SpO_2) signal at 1 Hz and detects respiratory events by an offline automated analysis algorithm. The respiratory disturbance index (RDI) is defined as the number of respiratory events per hour during which the SpO_2 decreases by 4% compared to the basal saturation of oxygen. This is automatically observed and measured by the offline automated analysis algorithm.

Evaluation of respiratory function

On the day preceding the administration of each of the epidural injections, the subjects had an appointment with a laboratory technician of the sleep clinic who explained to them the operating mode of the Remmers Sleep Recorder.

Subjects were asked to use the Remmers Sleep Recorder for three nights starting the night preceding the epidural injection (day 0) and the following two nights (day 1 and day 2).

For each treatment, the RDI, the mean oxygen saturation (SpO_2m) and the lowest SpO_2 were recorded. The severity of the respiratory function disturbance was assessed based on the RDI (<5: normal; 5-15: mild; 15-30: moderate; >30: severe)

Evaluation of pain intensity

Subjects were asked to evaluate their pain intensity daily in the evening, starting one day before the scheduled epidural injection (day 0) and for the next 14 days after the epidural injection. Subjects were asked to note their pain intensity using a 0 to 10 visual analog scale, where 0 represents no pain and 10 represent the worst pain imaginable.

Evaluation of side effects as a secondary outcome

Subjects were handed a logbook and asked to record for 14 days after each epidural injection any of the following side effects: pruritus, nausea, vomiting, and urinary retention.

Results

Out of the 34 patients recruited to participate to the study, four were excluded before randomization because they did not meet the inclusion criteria. Of the remaining 30 eligible patients, all agreed to participate. Three patients did not finish the trial treatment because they did not need a second injection, and they were excluded from the analysis.

Comparisons of the baseline variables of the randomized groups (A|B and B|A) are represented in Table 1. There were no significant differences in distribution by age, weight, height, gender, history of hypertension or cardiovascular disease, basic opioid treatment, or apnea.

Respiratory functions

As for the respiratory functions, there was no significant difference between morphine and morphine combined with naloxone on SpO_2m, lowest SpO_2, and on RDI between either group when naloxone was given as the first or second treatment. Over the two days following the

Variables		Group B|A	Group A|B	p-value*
		(N=14)	(N=13)	
Age†	Mean (SD)	54.7 (11.22)	58.2 (13.16)	0.4557
Weight (Kg)	Mean (SD)	78.4 (15.49)	77.8 (20.24)	0.9338
Neck circumference (cm)† Mean (SD)	38.2 (3.6)	35.2 (3.83)	0.0422	0.422
BMI†	Mean (SD)	26.41	28.66	0.227
Gender§	Men (%)	8 (57.1%)	3 (21.4%)	0.1201
	Women (%)	6 (42.9%)	11 (78.6%)	

History of hypertension (p=0.1266), history of cardiovascular disease (p=0.6217), history of snoring (p=0.8187), history of apnea (p=0.5134).
Treatment A: morphine 1 mg + bupivacaine 10 mg injection
Treatment B: morphine 1 mg + naloxone 0.08 mg + bupivacaine 10mg injection
*p-values based on §-Fisher's exact test, †-ANOVA and ‡-Chi-square test.
Table 1: Comparison of baseline variables.

treatment, no significant difference from baseline was observed for the SpO_2m, lowest SpO_2, and the RDI for both treatments. There was no carry-over effect on respiratory depression over the 14 days of the trial for both treatments. There was no significant carry-over effect on SpO_2m, lowest SpO_2, and RDI. There was no apparent correlation between daily dose of morphine administered orally or by dermal patch and SpO_2m, lowest SpO_2, or RDI. The percentage of patients with RDI <5 and RDI >15 was similar at day 0, day 1 and day 2 in both treatments. Similar results were obtained for SpO_2m. This demonstrates that there was no statistically significant effect of morphine or morphine combined with naloxone on the respiratory parameters. Bland and Altman plots showed differences in the RDI between the morphine and morphine combined with naloxone groups at day 0, day 1, and day 2 (Figure 2A-C) as well as in the SpO_2m between these two groups at day 0, day 1, and day 2 (Figure 3A-C). On day 0, the mean RDI and SpO_2m of the two treatment groups were not significantly different; as well, there was no statistically significant difference in their mean RDI and SpO_2m at day 1 and day 2.

Pain assessment

As for pain assessment, there was no significant gender effect in pain intensity. There was also no significant carry-over effect on pain intensity and side effects. Both treatment groups (morphine and morphine combined with naloxone) presented a significant difference in pain intensity compared with baseline during 14 days ($p< 0.005$ for morphine in both groups and $p<0.001$ for morphine combined with naloxone for both groups). Pain decreased by half from baseline pain at day 2 in 50% of subjects receiving morphine combined with naloxone, while for 50% of subjects receiving morphine alone, it was at day 6. Morphine combined with naloxone seemed to decrease pain more than morphine alone, but the result was not significant (p=0.2116). Basic opioid treatment did not appear to affect the pain after epidural injections.

Side effects

There was no significant difference in vomiting, pruritus, and urinary retention between morphine and morphine combined with naloxone. About 50% of patients experienced pruritus after morphine or morphine combined with naloxone injection, but it disappeared at day 3 after injection in the morphine combined naloxone group, and at day 5 for the morphine group. Of patients, 25% and 35% had nausea and vomiting in the morphine combined with naloxone group and morphine group, respectively, while 30% and 35% presented urinary retention (no catheterization was performed) in both groups, respectively.

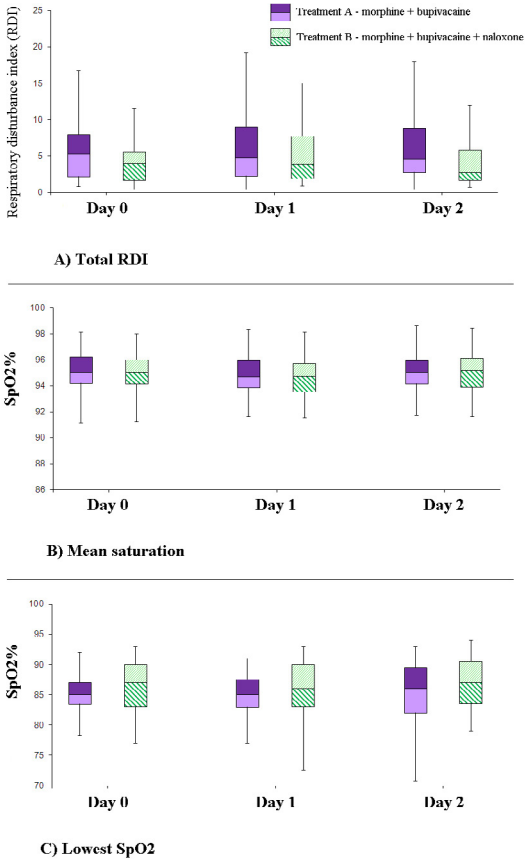

Figure 2: Respiratory function parameters.
A) Total RDI, B) SpO_2m, C) Lowest SpO_2.

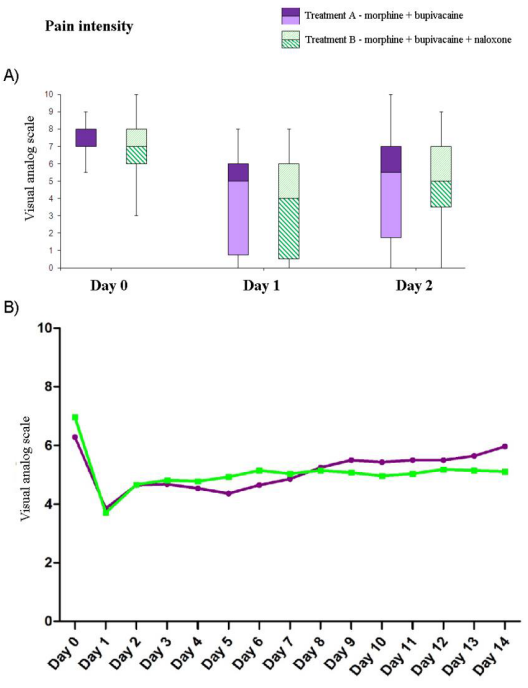

Figure 3: Pain evaluation.
A) Pain intensity at Day 0, 1 and 2,
B) Pain intensity over the 14 days of treatment.

Discussion

This study illustrates the effect of epidural mixture of morphine and bupivacaine combined with naloxone for management of chronic pain as well as the incidence of side effects such as hypoventilation, hypoxemia, nausea, vomiting, urinary retention, and pruritus. To our knowledge, this is the first trial to evaluate the occurrence of respiratory depression for three days, using both SpO_2 and RDI, after spinal injection of opioids for in patients with chronic back pain.

Morphine has low lipid solubility and delayed action after an epidural injection, which coincides with a peak concentration in the cerebrospinal fluid. Its relative hydrophilicity leads morphine to better penetrate the nervous system. Pre-synaptic and postsynaptic nerves in the subtantia gelatinosa of the posterior spinal cord, where there is a high density of μ receptors, are the major sites of action of opioids [13-16]. Studies have shown that epidural morphine analgesia may last for several days or even several weeks after a single injection [17-19]; therefore, epidural morphine is used as a treatment for chronic LBD.

The combination of bupivacaine plus morphine is an effective analgesic [5,20,21]. Because of this, we are not surprised that pain intensities were reduced in all the patients in both the case and control groups. Pain scores changes after injections were similar in both these groups. This finding is in agreement with previous publications.

Studies on the neuroaxial dose of morphine that causes respiratory depression shows that the occurrence of respiratory depression after intratechal injection is dose related with 0.3 mg of morphine producing little respiratory effect, 1 mg of morphine producing significant inhibition but still with maintenance of spontaneous ventilation, whereas 2.5 mg of morphine precipitated apnea [22,23].

We found no reduction in analgesia efficacy in patients receiving the low-dose epidural naloxone. Although, a new study shows adding naloxone to opioids prolongs the effect of analgesia in acute pain, we saw that the duration of analgesia did not increase in chronic pain. In our study, although the pain intensity differences in fourteen days in the two medication combinations are similar, the patients reported the pain decrease earlier when they received combination of morphine-bupocaine and naloxone. Actually, this finding supports the studies showing that the low dose neuroaxial naloxone improved analgesia [10,24]. Naloxone is a potent competitive antagonist of opioid mu-receptor. In theory, naloxone reverses the analgesic effect of morphine [25,26]. A review of the literature suggests that low-dose opioid antagonists can produce an antinociceptive or analgesic response. Moreover, it has been shown that in low doses, naloxone prevents post-opioid hyperalgesia and improves pain control [10,24,27]. There are various theories which explain the effects of low doses of naloxone on the analgesic effects of opioids: the upregulation of opioid receptors, increased levels of endogenous opioids, decreased opioid receptor coupling to stimulatory G-proteins, and an inhibition of opioid agonist-induced activation of glial cells [28,29]. In an animal model study, ultra-low dose naloxone enhanced the antihyperalgesia and antiallodynia effects of morphine in rats, possibly by reducing tumour necrosis factor-alpha, tumour necrosis factor receptor-1 expression, and excitatory amino acids (EAAs) such as glutamate and aspartate concentrations in the spinal dorsal horn [30,31]. One potential concern is the possibility of naloxone neurotoxicity [32]. The molecular structure of naloxone is very similar to morphine. In our study, the doses administered are of a very low concentration. In addition, researchers demonstrated that ultra-low dose naloxone attenuates glutamatergic transmission and neuroinflammation, and could thereby preserve the antinociceptive effect of morphine [31]. Intrathecal injection of 0.4 to 40 micrograms of naloxone blocked the analgesic effect of morphine in pain stimulation in an animal study [33]. Ultra-low dose naloxone reduces the TNF-α and TNFR1 expression in the rat and it enhances the antihyperalgesic and antiallodynic effects of morphine [34]. Reports differ as to the dose of epidural naloxone for use in man. One researcher used an epidural infusion of naloxone 0.004 mg per hour for caesarean section to evaluate its effect on pruritus [35]. Another study showed that the daily infusion dose of 0.05 mg combined with morphine could well control the patients' pain [36].

This study evaluated the effect of epidural naloxone on the side effects of epidural morphine while maintaining good analgesia. We consider that a reduction in the side effects can increase patient comfort. Although the efficacy of naloxone in reducing nausea, vomiting and pruritus while preserving the analgesic action of epidural morphine is well documented [10,24,35], we observed that our dose of epidural naloxone did slightly increase the incidence of nausea. Other studies have shown that epidural droperidol could reduce the incidence of morphine-induced nausea and vomiting [35,37]. Regarding the vomiting, pruritus, and urinary retention after epidural morphine analgesic in this study, the results were similar in both groups with or without naloxone.

We have shown that epidural low dose administration of naloxone, which acts as an antagonist at mu receptors, maintained analgesia without causing somnolence or a change in pruritus. There is limited knowledge on the dose-response relationship of naloxone when administered as neuroaxial analgesic. Although, human clinical trials are very rare, high-dose epidural administration of naloxone in mice reverses the analgesic effect of epidural morphine [38,39]; however, the other neuroaxial side effects of naloxone are not well known.

The pathophysiological effect of respiratory depression after systemic administration of morphine is the failure of the respiratory center to respond to hypercapnia and hypoxia. Consequently, the respiratory rate and the tidal volume are decreased [40,41]. In healthy volunteers, an epidural morphine dose-related respiratory depression (reduction in minute ventilation) was well documented [42,43]. Studies of patients with postoperative acute pain have shown that the incidence of respiratory depression is infrequent for doses commonly used clinically, but that it is dose-dependent for both hydrophilic and lipophilic opioids [44,45]. Many authors have reported that respiratory depression is very uncommon in patients previously made tolerant to opioids [45], findings that are in line with the present results. Moreover, patients with a normal respiratory rate can be hypoxic or hypercapnic when tidal volume is depressed with morphine [42,43]. For this reason, we monitored not only the respiratory rate but also SpO_2. To our knowledge, this is the first trial to evaluate the occurrence of respiratory depression after spinal injection of opioids among patients with chronic back pain using digital pulse oximetry at home. No correlation was found between the RDI and SpO_2m and the dose of morphine taken orally or cutaneously as a daily basic opioid treatment by patients. At a 0.08 mg epidural naloxone dose, we did not find any significant difference in the lowest SpO_2, SpO_2m, and RDI in the control group.

We conclude that epidural administration of naloxone improved patient comfort with no significant effect on pruritus, nausea, hypoxic episodes, and respiratory depression. So far, we cannot conclude that any changes in the doses could produce fewer side effects without interfering with analgesia. More human studies are needed to determine the ideal dose of epidural naloxone.

Conclusion

This randomized double-blind clinical trial shows that a single dose of 1 mg of epidural morphine combined with bupivacaine is an effective treatment for chronic LBP. Epidural morphine action is effective for more than several weeks. A 1 mg epidural dose of morphine does not cause any change on respiratory parameters in the subjects. A 0.08 mg dose of naloxone has no inhibitory effects on the analgesic activity of epidural morphine. Moreover, the low dose naloxone (0.08 mg) slightly enhanced the analgesic effect of morphine over a two-week period; however, the result was not significant. Additional studies are needed to evaluate the effects of different doses of epidural opioid-antagonist combined with opioids and to determine the optimal dose of naloxone.

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Disclosure

The authors declare no financial disclosure.

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