

# Neostigmine does not enhance the analgesic effect of morphine following arthroscopic knee surgery

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## Citation

E Kesimci, I Aysel, M Uyar, O Eris. *Neostigmine does not enhance the analgesic effect of morphine following arthroscopic knee surgery*. The Internet Journal of Anesthesiology. 2008 Volume 20 Number 2.

## Abstract

The aim of this study was to evaluate the analgesic efficacy of two different intraarticular injections; morphine and/or neostigmine. Sixty patients scheduled for arthroscopic knee surgery under general anesthesia were randomly allocated into four groups at the end of the surgery to receive morphine 2 mg (Group M), neostigmine 500 µg (Group N), morphine 2 mg and neostigmine 500 µg (Group MN) and 20 mL saline (Group S) intraarticularly. Visual analog scale (VAS) scores, analgesic consumption and side effects through 24 hours were recorded postoperatively. VAS scores were lower in the first three groups, while total analgesic consumption was significantly lower in Group M ( $p < 0.05$ ). Side effects did not differ between the groups. Although intraarticular neostigmine provided pain control and diminished analgesic use compared to placebo, the combination of neostigmine and morphine did not result in a comparable postoperative pain score and analgesic use with morphine alone.

## INTRODUCTION

Intraarticular drug administration is a popular technique for postoperative analgesia after arthroscopic knee surgery [1]. Although local anesthetics are the most common drugs which establish the efficacy of intraarticular injection for postoperative analgesia, the identification of opioid receptors on the peripheral sensory nerves, particularly in inflamed tissues, prompt investigators to explore the potential clinical application of intraarticular opioids [2]. Several studies have revealed long-lasting analgesia after a single intraarticular morphine injection following arthroscopic knee surgery, but other investigators have failed to demonstrate this analgesic efficacy [3,4]. These contradictory findings lead to assess whether the analgesic effect of intraarticular morphine is dose dependent or due to its systemic absorption rather than its peripheral effect. Moreover, the analgesic effect of morphine alone usually occurs late, so the majority of the studies have addressed agents combined with morphine to establish additive early effects [5]. Intraarticular administration of acetylcholinesterase inhibitor, neostigmine, has been demonstrated to result in a dose-dependent analgesia in patients undergoing knee arthroscopy, by elevating endogenous acetylcholine [1]. However, whether morphine and neostigmine act synergistically at peripheral sites is currently unknown. Thus, this clinical trial was designed to determine the effect

of adding neostigmine to morphine intraarticularly, on pain scores and analgesic consumption for arthroscopic knee surgery.

## Materials and methods

After obtaining local ethics committee approval and informed patient consent, 60 ASA group I-II patients scheduled for arthroscopic knee surgery were enrolled in the study. Patients taking analgesics within the last 24 hours before the study or patients with a history of allergic reaction to any of the study drugs, or cardiac, respiratory, hepatic and renal failure were excluded from the study. Before surgery all patients were instructed with regard to the use of patient controlled analgesia pump (PCA). No preanesthetic medication was administered. A 22 G intravenous cannula was inserted on the dorsum of the hand and a 5 ml.kg<sup>-1</sup>.h<sup>-1</sup> infusion of normal saline solution was started on admission to the operating room. Standard anesthesia monitoring including electrocardiography, non-invasive blood pressure and peripheral oxygen saturation (Hewlett Packard Anaesthesia Viridia 24 C) was performed. Subsequently anesthesia was induced by propofol 2 mg.kg<sup>-1</sup> IV and fentanyl 2 µg.kg<sup>-1</sup> IV, and endotracheal intubation was facilitated by administration of vecuronium 0.1 mg.kg<sup>-1</sup> IV. Anesthesia was maintained with 66% nitrous oxide in oxygen and 1-2 % isoflurane. Mechanical ventilation was

used in all patients to maintain an end-tidal carbon dioxide concentration of 32-36 mmHg. No further opioids were administered intraoperatively. When the surgical procedure was completed, intraarticular solution was administered by the surgeon before removal of the arthroscope. From a list of random numbers, instructions for randomization were prepared in sealed envelopes for each patient before start of the study. The patients were allocated to one of the four groups in a double-blind manner so as to receive either morphine 2 mg in 20 mL saline (group M) (n = 15), neostigmine 500 µg in 20 mL saline (group N) (n = 15), morphine 2 mg with neostigmine 500 µg in 20 mL saline (group MN) (n = 15) or 20 mL saline (group S) (n = 15). After the intraarticular injection, tourniquet was kept inflated for an additional 10 min. Following extubation postoperative pain was treated by patient-controlled analgesia pump with morphine using a 0.3 mg.h<sup>-1</sup> basal infusion rate, 1 mg bolus dose and a 15 minute lockout interval in the clinic of orthopaedic surgery for 24 hours. A 10 cm linear VAS was used to assess pain (0 cm: no pain; 10 cm: the worst imaginable pain). Pain scores at 1, 2, 4, 12 and 24 h and, total morphine consumption (mg) at 24 h were recorded by an anesthesiologist blinded to the drug preparation and patient group assignment.

Data analysis was performed by SPSS 11.0 for Windows. Statistical analysis used Friedman test, Wilcoxon, Kruskal-Wallis, Mann-Whitney U, Repeated ANOVA tests. Bonferroni adjustment was made for multiple comparisons. Significance was determined at the P< 0.05 level.

## RESULTS

Demographic and operational data were similar (Table 1).

### Figure 1

Table 1: Demographic data and surgical characteristics

	Group M (n = 15)	Group N (n = 15)	Group MN (n = 15)	Group S (n = 15)	P
Sex (Female/Male)	4 / 11	6 / 9	2 / 13	5 / 10	NS
Age (yr)	46.1 ± 12.1	37.8 ± 7.9	35.4 ± 9.5	35.8 ± 12.6	NS
Weight (kg)	73.1 ± 12.3	77.1 ± 12.4	74.1 ± 12.1	75.5 ± 13.1	NS
Duration of surgery (min)	64.3 ± 35.8	68.3 ± 46.1	48.6 ± 17.6	47.5 ± 16.7	NS
Duration of anesthesia (min)	84.6 ± 16.6	89.6 ± 23.4	79.6 ± 19.7	79.0 ± 18.1	NS

NS = not significant, values are mean ± SD or n

VAS scores at 24 h were lower in the first three groups compared with intraarticular saline group, but no significant difference was documented between the treated groups

(Table 2). There was a significant difference with respect to morphine consumption among the groups (p< 0.05). Total morphine consumption was significantly lower in Group M compared to Group N and MN at 24 h. Group N consumed more morphine than Group MN at 24 h (p> 0.05). All patients in Group S needed significantly more morphine than the study groups (Table 2).

### Figure 2

Table 2: Pain scores and total morphine consumption (mg) at 24 h

	Group M (n = 15)	Group N (n = 15)	Group MN (n = 15)	Group S (n = 15)	P
1 h VAS	2.7 ± 2.3	3.1 ± 2.7	1.8 ± 1.5	3.7 ± 2.1	NS
2 h VAS	1.7 ± 1.6	2.5 ± 2.7	1.7 ± 1.6	3.0 ± 1.8	NS
4 h VAS	1.7 ± 1.6	2.3 ± 2.3	1.3 ± 1.3	2.5 ± 1.6	NS
12 h VAS	1.5 ± 1.1	1.7 ± 1.9	1.6 ± 1.0	1.8 ± 1.9	NS
24 h VAS	1.1 ± 1.3	1.3 ± 1.6	1.2 ± 1.3	1.3 ± 1.9	NS
Morphine (24 h total)mg	8.2 ± 3.1	18.6 ± 7.2	14.9 ± 7.2	21.1 ± 7.3	*

NS = not significant, values are mean ± SD or n

\* Group M versus Group N, Group MN and Group S p < 0.05; Group S versus Group M, Group N and Group MN p < 0.05

There were no significant differences between groups in terms of sedation scores, respiratory and hemodynamic parameters (p>0.05). No patient was treated for pruritus, nausea or other side effects.

## DISCUSSION AND CONCLUSIONS

In the current study, we evaluated the analgesic benefit from the individual and combined intraarticular administration of neostigmine and morphine following knee surgery. The overall pattern in all patients demonstrated less postoperative pain and analgesic use than the control group during the first 24 hours. However, the data do not support the conclusion that addition of neostigmine to morphine provided even more effective analgesia.

The demonstration of the existence of opioid receptors in the peripheral tissues has focused on a new rationale for perioperative pain control [8]. In animal experiments and clinical studies, effective and relatively long-lasting postoperative analgesia has been confirmed with administration of intraarticular morphine compared with placebo in arthroscopic knee surgery [9,10,11]. Accordingly, these studies have revealed that morphine acts via peripheral receptors to induce analgesia in humans. However, there exists a wide variability in the analgesic effect of intraarticular morphine among the studies. Likar et al.

demonstrated dose dependent analgesic effect of morphine in a study in which three doses of morphine (1, 2, and 4 mg) were injected intraarticularly [12]. In two other studies, Kanbak and Richardson found improved analgesia after 5 mg morphine [13,14]. In contrast to these three investigators recently, Tetzlaff found equivalent analgesia with 1 vs 3 mg morphine [15]. While these results are suggestive, some of the studies do not support the analgesic effect of locally injected morphine [6]. Moreover, some studies suggest early beneficial effects, whereas others report only late effects. To explain the cause of this variability seen between studies; either differences in the dose of morphine used intraarticularly or the degree of intraarticular inflammatory process must be postulated. Furthermore, the potential effect of intraarticular morphine may be dose dependent and also a systemic effect cannot be excluded.

In our study we used 2 mg intraarticular morphine because most of the experience is based on the range of 1 mg to 5 mg in the literature. This dose not only decreased postoperative pain intensity, but also reduced analgesic consumption up to 24 hours after the injection when compared with placebo. However, one of the important aims of this study was to quantify the effect of morphine versus neostigmine -an active drug-.

The spinal or epidural administration of the acetylcholinesterase inhibitor neostigmine results in a dose-dependent analgesia through stimulation of cholinergic receptors of the dorsal horn of the spinal cord. In a study, Lauretti et al hypothesized that the analgesia mediated by epidural neostigmine was not only due to drug spread into the CSF, but also to a supraspinal mechanism, thus resulting in a greater analgesic efficacy than peripheral neostigmine [16]. In rat inflamed knee joint Buerkle et al demonstrated enhanced levels of the endogenous neurotransmitter acetylcholine that seemed to act as one of a group of analgesia-modulating compounds at central and peripheral sites in inflammatory pain [9]. Duarte et al also confirmed this experimental data in laboratory animals [17]. Since then, neostigmine has been administered via intraarticular route for pain relief after arthroscopic knee surgery. However, studies of peripherally applied neostigmine are few and the efficacy of peripheral neostigmine remains speculative. In a study by Yang et al intraarticular 500µg neostigmine resulted in significant VAS reduction 1 h after injection with a long duration of analgesia (6 hours) compared with patients given intraarticular saline and morphine [1]. Similarly, in another study, Alagol et al. demonstrated that intraarticular

neostigmine provided analgesia for over 5 h [18].

Consequently, we used neostigmine 500 µg based on the clinical experience and frequent use on preference by the great majority of anesthetists. We documented neostigmine induced analgesia via low morphine consumption values after the end of surgery however; beneficial effects afforded by neostigmine were transient and did not support the findings of Yang and Alagol with respect to duration of analgesia, although we used the same doses. However, there is no clear explanation of the differences between our findings and other clinical studies. All patients in our study had minor-moderate orthopaedic procedures, but there is a probability that these procedures sometimes produce significant postoperative pain because the intensity of pain is variable from patient to patient apart from the type of surgery; so this may explain the lack of a longer duration of analgesia in neostigmine group.

Recently, it was shown that local anesthetics and adjuncts such as epinephrine, non-steroidal anti-inflammatory agents or  $\beta_2$  adrenergic agonists when combined with morphine enhanced postoperative analgesia by a peripheral mechanism [7,19]. However, there have been no published studies on the combination of intraarticular morphine and neostigmine. Our study failed to show any beneficial effect of neostigmine in combination with morphine. According to our results, the postoperative analgesic requirements were higher in the combined group compared with the morphine group. We cannot provide a definitive explanation for this finding; however we might speculate that despite the similarities between opioid and muscarinic analgesia, the mechanism by which morphine and acetylcholine produce analgesia in the CNS and in the periphery may be worth discussing [20]. In fact, while in the CNS acetylcholine seems to modulate the cGMP pathway through nitric oxide release, as it does in the periphery; morphine has shown to act through different mechanisms centrally and peripherally. More specifically, morphine would activate the cGMP pathway through NO release in the periphery, but in the CNS, would act on the same pathway with other mechanisms- still to clarify- than NO release [21]. Furthermore, when these two molecules administered at the level of the CNS, they may act synergistically because of having different sites/mechanisms of action [22]. However, when they are administered in the periphery, they may be competing for the same sites of action which might explain the reason of not observing a synergistic effect as in our study.

There is no study addressing this effect in the current

literature, thus we have to acknowledge that future studies are necessary to outline this interaction.

Although analgesia achieved by parenteral administration of morphine and neostigmine is attractive, side effects limit their use. We could not demonstrate any difference in the occurrence of adverse effects or changes in heart rate, blood pressure, respiratory parameters or sedation score.

In conclusion, morphine provided a strong evidence for reduction of postoperative pain and less analgesic consumption after arthroscopic knee surgery. Our findings do not encourage the use of neostigmine combined with a long acting opioid analgesic nevertheless; individual intraarticular use of neostigmine does not demonstrate a significant benefit on postoperative pain score and analgesic use. Further studies of the combinations of peripherally applied neostigmine and morphine are required before final recommendation.

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