PREOPERATIVE ORAL DEXTROMETHORPHAN DOES NOT REDUCE PAIN OR MORPHINE CONSUMPTION AFTER OPEN CHOLESYCTECTOMY

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Summary

Background: Dextromethorphan (DM), the D-isomer of the codeine analogue levorphanol, is a weak, noncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist. It has been suggested that NMDA receptor antagonists induce preemptive analgesia when administrated before tissue injury occurs, thus decreasing the subsequent sensation of pain.

Method: The study was conducted in the Dr Ali shariati hospital, Tehran University of Medical Sciences, Tehran, Iran. In this seventy two patients scheduled for elective cholesyctectomy between February 2005 and December 2006 were randomized into three equal groups to receive as premedication either oral dextromethorphan 45 mg (Group D45 = 24), dextromethorphan 90 mg (Group D 90 = 24) or placebo (Group C, n = 24), 120 min before surgery. A visual analogue scale (VAS) for pain of each patient measured at arrival in the ward and 6 and 24 hours after surgery, was recorded.

Results: The demographic characteristics of patients, ASA physical status class, duration of surgery, and the basal VAS pain score were similar in the two groups. There was no significant difference in the mean of the VAS pain scores measured over time or morphine consumption between three groups.

Conclusion: Dextromethorphan, 45 and 90 mg orally administrated 2 h before surgery had no effect on postoperative morphine requirement and pain intensity.

Key words: dextromethorphan, postoperative pain, preemptive analgesia.

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Introduction

Opioids, are frequently administered to patients undergoing major surgery to alleviate postoperative pain. However, they may cause adverse effects such as nausea and vomiting, pruritus, urinary retention and respiratory depression[1].

As the analgesia and side effects of opioids are dose dependent, a multimodal offset may enhance analgesia while minimizing the side effects[1]. Dextromethorphan (DM), the D-isomer of the codeine analogue levorphanol, is a weak, noncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist that has been used as an antitussive drug for more than 40 years[2,3]. It has been suggested that NMDA receptor antagonists induce preemptive analgesia when administrated before tissue injury occurs, thus decreasing the subsequent sensation of pain[2,3].There is good evidence from basic scientific literature to believe that acute postinjury pain states in humans could be treated usefully with a combination of opioids and NMDA antagonists[46-].

The purpose of the current study was therefore to determined to find out whether preoperative administration of 45 and 90 mg of oral DM would reduce postoperative pain and opioid consumption as compared to a control group.

Method & Materials

The study was conducted in the Dr Ali shariati hospital, Tehran University of Medical Sciences, Tehran, Iran.

The proposal was approved by the Institutional Ethics Committee and informed written consent was obtained from the patients. Between February 2005 and December 2006 seventy two patients, 25-50 years, ASA I & II scheduled for open cholesyctectomy (midline approach) under general anesthesia, were enrolled in this randomized, double- blinded, and placebo controlled study.

Patients who received opioids within 48 h of surgery and sedatives or centrally acting drugs(central nervous system depressants or antidepressants) during the 21 days prior to surgery; those with a history of chronic pain, psychotic disorders or addiction including opioids, those with any contraindication to DM and pregnant or lactating women were excluded from the study.

All participants were given full explanations of DM and the visual analog scale for pain (VAS) on the day before surgery.

All drugs were given by an anesthesiologist who was not involved in patient observation, thus both the observer and patients were blinded to the group assignment. Patients were randomly assigned into three equal groups (24 each): Patients receiving DM 45 mg (Group 45 DM), (Patients receiving DM 90 mg (Group DM 90, and (Group C) using a computer generated randomization list.

All patients in the 3 groups received the designated dose orally 120 min before surgery. Placebo was in similar capsules containing sucrose.

On arrival to operating room, all patients were 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.

Anesthesia was induced with 2 $mg.kg^{-1}$ propofol and 0.3 $\mu g.kg^{-1}$ sufentanyl; and endotracheal intubation was facilitated with 0.15 $mg.kg^{-1}$ cisatracurium. After tracheal intubation, anesthesia was maintained by isoflurane and N_2O (50%); 0.05 $mg.kg^{-1}$ cisatracurium and 0.2 $\mu g.kg^{-1}$ sufentanyl were administered half hourly. Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.7-5.3 kPa). Patients were actively warmed to keep core temperature (esophageal) normothermic. At the beginning of the skin sutures, drugs administration was stopped and neuromuscular block was antagonized by IV administration of 2.5 mg of neostigmine along with 1.25 mg atropine. Patients were considered awake when they opened their eyes on demand or after gentle tactile stimulation; they were later extubated.

The severity of postoperative pain was measured and recorded using a 10-cm visual analog scale (VAS), (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 6 and 24 hours after surgery. Patients could request rescue analgesia at any time. Morphine, 0.1 mg/kg-1 was given as rescue analgesia at 8-h intervals.

According to the previous studies, a sample size of 24 in each group would be sufficient to detect a difference of 3 scores in the mean of pain score, estimating a power of 80%, and a significance level of 5%. Statistical analysis was performed using SPSS package (SPSS Inc., Chicago, IL, USA), version 11.5. Normality of distribution was checked as needed. For statistical analysis of demographic data and for comparison of groups one way ANOVA, repeated measure analysis of variance, Fishers exact or Chi-square tests where appropriate. Tow tailed $P<0.05$ was taken as significant.

Results

Seventy two patients were randomized. Three patients were excluded from the study because the surgical complications (two from C group and one from D45 group).

Demographic characteristics of patients, ASA physical status class, and surgery time (min) were similar in the two groups (Table 1).

Table 1
Demographic characteristics

	Group Control (n = 22)	*Group DM 45 (n = 23)*	*Group DM 90 (n = 24)*
Age (yr)*	48.3 ± 14.5	48.2 ± 14.3	46.2 ± 23.3
Sex (F/M)	13/9	13/10	14/10
Surgery Time (min)*	98 ± 25.6	104 ± 23.2	112 ± 13.2
ASA class (I/II)	10/12	12/11	11/13
Weight (kg)*	78.3 ± 7.5	80.1 ± 10.4	75.1 ± 8.3

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

There were no significant differences in the mean of the morphine consumption (12.39 ± 5.24 mg in DM 45 group and 13.71 ± 4.28 mg in DM 90 group, versus 11.88 ± 5.29 in C group) and the time to first morphine request (3.1 ± 1.7 h in DM 45 group and 3.2 ± 1.9 in DM 90 group, versus 2.9 ± 1.1 in control group) (Table 2).

There was no significant difference in the mean of VAS pain scores measured over time between three groups(5.55 ± 1.38, 4.83 ± 2.39, 3.62 ± 2.92 in group C; 4.73 + 2.14, 4.22 + 2.36, 4.00 + 2.50 in group DM 45; and 5.18 ± 2.81, 4.12 ± 2.80, 3.24 ± 2.95 in group DM 90, repeated-measures analysis of variance, between-subjects effects) (Table 2).

Table 2
VAS for pain, morphine consumption and time to first morphine injection in the three groups.

	Group Control	*Group DM 45*	*Group DM 90*
Total Morphine Consumption (mg)*	11.88 ± 5.29	3.1 ± 1.7	3.2 ± 1.9
Time to First Morphine Injection (h)*	2.9 ± 1.1	12.39 ± 5.24	13.71 ± 4.28
Visual Analogue Scale for pain*			
- Arriving Ward	5.55 ± 1.38	4.73 + 2.14	5.28 ± 2.81
- 6 h	4.83 ± 2.39	4.22 + 2.36	4.12 ± 2.80
- 24 h	3.62 ± 2.92	4.00 + 2.50	3.24 ± 2.95

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

Discussion

This study demonstrated that in patient undergoing open cholecystectomy, oral premedication with 45 or 90 mg DM did not decrease post-operative pain intensity or morphine consumption when compared to patients who received placebo. Our findings are not consistent with earlier reports that dextromethorphan reduces pain and analgesic requirement after various surgeries[7-10].

N-methyl-D-aspartate receptor antagonism inhibits wind up or central hypersensitivity of dorsal horn neurons in response to noxious stimulation[2-11]. Dextromethorphan, an NMDA receptor antagonist has been shown to reduce secondary hyperalgesia but have no effect on primary hyperalgesia on healthy adult male volunteers[2,12,13].Other investigators have been unable to demonstrate that DM, in clinically relevant dose, has any effect on primary or secondary hyperanalgesia[14,15].

The ability of DM to attenuate pain is controversial. Not all investigators agree that DM reduces opioid consumption or acute pain. Although DM have been used successfully as premedication for postoperative pain and morphine consumption reduction in some investigations[6-10], other studies have not corroborated these reports[16-19].

Ilkjaer et al studied 50 patients undergoing non-malignant elective abdominal hysterectomy. The study was a double-blinded, randomized designed to compare

post-operative analgesia requirements and pain scores in patients who received preoperative DM or placebo. DM reduced morphine requirements in this sample and a modest (but non-significant) reduction in pain scores was found. They found that oral dextromethorphan 150 mg reduced PCA morphine consumption immediately (0-4 h) after hysterectomy, without prolonged effects on pain or wound hyperalgesia[18].

Thematic of the controversy surrounding the role of DM in acute pain management, Wadhaw et al. failed to demonstrate the specific opioid sparing effect expected with DM administration. In this 66 patient experimental sample, the investigators concluded that DM dose not improve acute pain scores even at high doses[19].

Many surgical procedures were included in both positive and negative studies, and there did not appear to be one specific procedure that yielded more benefit than any other. In the dextromethorphan studies, four negative studies used the oral route, and in two of these trials at smaller doses of drug, there was no direct analgesic effect of the intervention[16-19].

The NMDA blocking properties of DM are likely less potent compared to ketamine[2]. It is possible that only subset of individuals will benefit from the NMDA properties of DM.

As well it may be that DM should be administered parenterally in a dose of at least 1 mg/kg^{-1} for maximal preventive effect[2].

Further investigations are required to determine whether larger doses or repeated doses of oral dextromethorphan attenuate post operative pain. However, undesirable side effects of dextromethorphan, including sedation and ataxia, are common in adults when the dose is increased above that recommended for antitussive therapy and may limit its usefulness[17].

The power analysis for this study indicated that there were sufficient numbers of patients in each group to detect 25% reduction in morphine use and 30 mm reduction in VAS for pain on moving.

In conclusion, dextromethorphan, 45 and 90 mg orally administrated 2 h before surgery had no effect on postoperative morphine requirement and pain intensity.

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