

Original Article**Premedication with oral Dextromethorphan reduces intra-operative Morphine requirement***R. Talakoub MD*, F. MolaeinasabMD****ABSTRACT**

Background: Intra-operative pain has adverse effects on hemodynamic parameters. Due to complications of opioids for pain relief, using non-opioids medication is preferred. The purpose of this study was to investigate the effect of oral dextromethorphan premedication on intra-operative Morphine requirement.

Methods: After approval of the Ethics committee and informed consent, 40 adult patients who stand in American Society of Anesthesiologists Physical Status I and II, under general anesthesia for elective laparotomy were selected and classified in two equal groups randomly. In group A, oral dextromethorphan (60mg) was administered at 10 PM and 6 AM preoperatively. In group B, placebo (dextrose) was administered. After induction of general anesthesia and before skin incision, intravenous morphine (0.01 mg/kg) was administered. During surgery, when systolic blood pressure or heart rate was increased more than 20% of the preoperative baseline, 0.01 mg/kg morphine was administered. At the end of surgery, the totally prescribed morphine (mg/kg) and maximal increase in systolic, diastolic, mean arterial blood pressure and heart rate relative to the baseline values were calculated and statistically compared with student's t-test.

Results: The mean dose of administered morphine during surgery was significantly less in group A than group B ($P < 0.0001$). Also, Maximal increase in systolic, diastolic and mean arterial blood pressure was significantly less in group A ($p < 0.003$, $p < 0.004$, $p < 0.0001$, respectively). There was no significant difference in maximal heart rate increase between two groups ($p < 0.114$).

Conclusion: Oral dextromethorphan premedication may decrease intra-operative morphine requirement and reduce maximal increase in systolic and mean arterial blood pressure during surgery.

Key words: Dextromethorphan, Morphine, Intra-operative, Premedication Hemodynamic

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Physiologic responses to injury and stress including pulmonary, cardiovascular, gastrointestinal, neuroendocrine and metabolic changes, urinary dysfunction, impairment of muscle metabolism and function can be eliminated or reduced with currently available analgesic techniques¹. Therefore improved methods for intra-operative analgesia are desirable.

Preventive analgesia is an antinociceptive treatment before tissue injury that prevents the establishment of altered central nociception processing which amplifies operative pain, and improves pain management².

Central sensitization -mainly results from the activation of N-Methyl-D-Aspartate (NMDA)

receptors in the central nervous system- was triggered by long-lasting nociceptive afferent input. Hence, NMDA antagonists (dextromethorphan and ketamine) may prevent the induction of central sensitization³. This property has led to its experimental use in a number of clinical areas, such as acute⁴⁻⁶ and chronic pain⁷, and neuroprotection after brain injury⁸.

Kawamata reported that premedication with dextromethorphan before and after surgery had a significant reduction in some pain scores at rest and less analgesic requirement till 48 hours after operation⁴.

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In This study, we investigated the effect of oral dextromethorphan premedication on intra-operative pain by assessing its effect on analgesic requirement after laparotomy.

Materials and Methods

After approval of the Ethics committee and obtaining patients written informed consent, 40 patients scheduled for elective laparotomy under general anesthesia were enrolled in this investigation.

The inclusion criteria were 1- age >18 years old and 2- American Society of Anesthesiologists Physical Status I and II (ASA-PS I & II). Exclusion criteria included the consumption of monoamine oxidase inhibitors, quinidine, tricyclic antidepressants, hepatic diseases, addiction to opioids and known allergy or contraindications to the test drug and morphine. The patients were randomly assigned to double-blind administration from coded capsules. Both groups received two identical capsules at 10 pm and 6 am preoperatively. Each capsule contained 60 mg dextromethorphan or dextrose (placebo).

General anesthesia was induced with fentanyl (2 µg/kg), thiopental (6mg/kg) and pancronium (0.1 mg/kg) in both groups. After intubation anesthesia was maintained with halothane 0.7-1% and nitrous oxide 50% in Oxygen.

The systolic, diastolic, mean arterial pressure (MAP) and heart rate (HR) were measured and recorded one hour before and every five minutes during the operation. During operation if the systolic blood pressure and/or heart rate increased more than 20% of basic values (one hour before operation), morphine (0.01mg/kg) were injected intravenously every 5 minutes till maximal dose of 0.15 mg/kg or the increase in systolic blood pressure or heart rate become less than 20% of basic values. The fluid therapy was according to the 4, 2, 1 law and the blood lost was compensated by giving 3 ml of ringer for each 1 ml blood lost. If the blood lost was more than the maximal allowed blood lost (MABL), for each ml of blood lost, 1 ml of packed RBC were given.

At the end of operation the total morphine consumption and the maximal increase in systolic, diastolic, MAP and HR were measured and the data were analyzed by using student's t-test with a p value < 0.05 regarded as significant.

Results

Forty adult patients (20 in each group) met the criteria. There was no significant difference in age, frequency of sex, ASA group and site of laparotomy, preoperative hematocrit value and the duration of operation between two groups (p>0.05) (Table -1).

Table 1. The characteristics of dextromethorphan and placebo groups

	Dextromethorphan N=20	Placebo N=20	P- value
Male	60%	55%	P<0.74
Female	40%	45%	
Age (years)	46.2 ± 15.93	50.45 ± 14.57	P<0.384
ASA I	65%	65%	
ASA II	35%	35%	P=1
Duration of operation(min)	114 ± 45.73	129.5 ± 51.35	P<0.32
abdominal surgery:			
Upper	60%	55%	
Lower	40%	45%	P< 0.074

Mean maximal increase in systolic, diastolic, mean arterial pressure, and mean morphine consumption during operation were significantly different between two groups ($p < 0.05$).

But, maximal increase in heart rate during operation was not different between groups ($p < 0.114$) (Table -2).

Table 2. Homodynamic parameters and dosage of drugs in case and control groups

	Dextromethorphan	Placebo	p-value
Mean morphine consumption	0.086 ± 11	0.1006 ± 0.011	P<0.01
Mean maximal increase in :			
Systolic blood pressure	25.62 ± 8.616	36.25 ± 12.35	p<0.003
Diastolic blood presser	15.5 ± 7.776	23.5 ± 8.599	p<0.004
Mean arterial pressure	19.15 ± 6.753	28.25 ± 8.025	p<0.0001
Heart rate	20.4 ± 6.676	23.85 ± 6.823	p<0.114

Discussion

Our study showed that a double preoperative doses of dextromethorphan (120 mg orally) has a significant effect on reduction of systolic BP, diastolic BP, MAP and the morphine consumption during operation, which is in agreement with others studies.

The difference between mean morphine consumption in both groups is statistically significant ($p < 0.05$). Also, the hemodynamic changes were less in dextromethorphan group than controls.

The abundant research demonstrates the efficacy of dextromethorphan on post-operative pain. Ching-Tang Wu showed that pre-incident dextromethorphan treatment offers preemptive analgesic effect, improving the postoperative pain management after laparoscopic cholecystectomy¹⁰. Yuan-Yi chia demonstrated that preoperative administration of intravenous dextromethorphan reduces post-operative morphine consumption after abdominal surgery¹¹. Kawamata also showed

that premedication with oral dextromethorphan reduces postoperative pain after tonsillectomy⁴. Other studies demonstrated the uneffectiveness of dextromethorphan in the postoperative pain and analgesic requirement after total abdominal hysterectomy⁵, and adenotonsillectomy¹².

These results can not be comparable with our findings because the perception of postoperative pain can be influenced by the psychosocial background of patients which does not affect the intraoperative pain under general anesthesia¹.

According to our findings, we conclude that the preoperative dextromethorphan reduce morphine consumption and stabilize hemodynamic state during operation. These effects may be due to the non-comparative analgesic effect of dextromethorphan on NMDA receptors and the inhibition of wind-up phenomena and pain receptors via posterior nerve of spinal cord³.

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