Pre-emptive oral dextromethorphan reduces both postoperative and packing removal pain in patients undergoing nasal surgery

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ABSTRACT

الأهداف: تقييم كفاءة عقار الدكستروميثورفان (45mg)، بتناوله قبل عمليات الأنف في تخفيف الألم بعد هذه العمليات في ظل وجود حشو أنفي وعند نزع الحشو.

الطريقة: أجريت هذه الدراسة في مستشفى الموسى العام – الإحساء – المملكة العربية السعودية، خلال الفترة مابين يناير 2007م وحتى مارس 2008م. تلقي 38 مريضاً بعمر (11±28) (DM) عن طريق الفم، فيما تلقى 38 مريضاً آخر بعمر (11±26) عقار مموه (بلاسيبو). تم قياس درجة الألم عند المرضى باستخدام المقياس المرئي التناظري، وعند وصول درجة الألم إلى (5≤) تم إعطاء (2mg) مورفين عن طريق الوريد كل 10 دقائق وذلك في وحدة الإفاقة (PACU)، وبمقدار (1gm) باراسيتامول عن طريق الوريد قسم الجراحة على تنخفض درجة الألم إلى (5>). كما يتم مراقبة درجة الألم عند نزع الحشو الأنفي.

النتائج: كانت درجة الألم مرتفعة في المجموعة التي تلقت عقار (بلاسيبو) في قسم الإفاقة (PACU) كما تلقت جرعات مرتفعة من المورفين عنها في مجموعة (DM) (2.6 ± 7.3mg) مقابل (p=0.03) (1.2 ± 4.6mg). كما كانت درجة الألم مرتفعة في المجموعة التي تلقت عقار (بلاسيبو) في قسم الجراحة في 4, 8, 12, 24 ساعة ولكن بصورة غير مهمة، بينما كان أقل بعد 18 ساعة (p=0.26). كانت درجة الألم مرتفعة في مجموعة (بلاسيبو) عن مجموعة (DM) عند نزع الحشو الأنفي (11±7.8 مقابل 15±3.5) (p=0.004).

خاتمة: استخدام عقار الدكستروميثورفان (DM) قبل عمليات الأنف يؤدى إلى تقليل استخدام المورفين ويؤدى إلى تقليل الألم المصاحب لنزع حشو الأنف.

Objectives: To determine whether premedication with 45 mg of oral dextromethorphan (DM) given 90 minutes prior to nasal surgery decreases postoperative pain and consequently reduces opioid administration and also, if it reduces the pain of pack removal.

Methods: This was a prospective, double blind, randomized, controlled study carried out from January 2007 to March 2008 at Al-Moosa General Hospital, Al-Ahsa, Saudi Arabia, in which 38 patients received oral DM (age 28 ± 11 years), and 38 patients received placebos (age 26 ± 10 years). Postoperative pain was assessed using a visual analog scale, and a pain score of ≥5 was treated by a rescue bolus dose of morphine sulfate 2 mg every 10 minutes in the post-anesthesia care unit (PACU) and by one gm of paracetamol in the surgical ward until the score became <5. Pain was also assessed during pack removal.

Results: The placebo group had a higher pain score in the PACU, and hence a higher morphine consumption than the DM group (7.3 mg ± 2.6 versus 4.6 mg ± 1.2, p=0.03). Pain score in the surgical ward was also higher in the placebo group at 4, 8, 12, and 24 hours, but this was insignificant, and was insignificantly lower only at 18 hours (p=0.26). The placebo group had a higher pain score at pack removal than the DM group (7.8 ± 11 versus 3.5 ± 15, p=0.004).

Conclusions: Preemptive medication with DM reduces opioid administration in the early postoperative period and during pack removal.

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Functional endoscopic sinus surgery (FESS) is assumed to be more comfortable and less painful to the patient; however, it is associated with mild to moderate postoperative pain which is related to both

the surgical trauma and nasal packing.[1] Noxious stimuli from peripheral tissue and/or nerve injury accompanying surgery are thought to develop neuropathic pain through the mechanism of central sensitization induction. Once central sensitization occurs, postoperative pain becomes difficult to treat.[2] Changes in sensory processing occur in the spinal cord where the dorsal horn neurons become hyperexcitable and the nervous system demonstrates an enhanced response to noxious stimulation.[2] Central sensitization is believed to result from activation of N-methyl-D-aspartate (NMDA) receptors in the spinal cord after triggering of these receptors by tissue injury.[3] To prevent such pain, preoperative NMDA antagonists have been tried with certain preferable effects, known as preemptive analgesia.[4-7] Dextromethorphan (DM), a non-opioid antitussive in clinical use for many years, is a non-competitive NMDA receptor antagonist with low affinity and is reported to show a preemptive analgesic effect. Premedication with oral DM (45 mg, administered 60 minutes before surgery) reduced postoperative pain after tonsillectomy in adults.[8] However, the results were conflicting in children.[9,10] Also, DM was used preoperatively in children undergoing tympanomastoidectomy with success in reduction of postoperative opioid administration.[11] The aim of this study was to determine whether administration of oral DM (45 mg) 90 minutes prior to nasal surgery (FESS and/or septoplasty) improves postoperative pain in the presence of the nasal packing, and to assess the pain during pack removal.

Methods. With approval for the study by the Al-Moosa General Hospital (Al-Ahsa, Saudi Arabia) ethics committee, and with patient's written informed consent, we enrolled 80 patients in this prospective, randomized, controlled, double blinded study from January 2007 to March 2008. Patients had ASA physical status I (18-54 years), who were scheduled for elective endoscopic sinus surgery and/or septoplasty under general anesthesia. All patients were taught how to use the visual analog scale (VAS) to express their postoperative pain degree 1-3 days before surgery. The VAS consists of a 10-cm baseline with 0=no pain and 10=worst imaginable pain. Patients with a history of significant cardiac, pulmonary, renal, or hepatic diseases, asthma, peptic ulcer, history of allergy to either DM or placebo syrup or on tranquilizers were excluded from the study. Also, patients who did not show reliability with VAS usage at time of explanation were excluded. Patients did not receive any analgesic drugs one day before surgery. Patients were assigned randomly to one of 2 groups in a 1:1 ratio, to receive either 45 mg DM syrup or placebo syrup approximately 90 minutes before surgery. The placebo syrup was chosen to be of same color (red) and tastes like the DM syrup and also, as an antitussive drug that does not contain DM (carbocysteine, Rhinathiol 5%, Sanofi Winthrop Industry, France). Endoscopic sinus surgeries (ESS) were in the form of polypectomy, middle meatal antrostomy, total ethmoidectomy, and sphenoidotomy. No other premedications were given. All patients received only intravenous (iv) anesthesia with propofol (2 mg/kg bolus, followed by a continuous infusion at 4-6 mg/kg/h) and remifentanil (infusion rate ranging between 0.1-0.25 μg/kg/min). Muscle relaxation with rocuronium (0.6 mg/kg) was given to facilitate tracheal intubation and mechanical ventilation. Standard monitoring was used, including ECG (lead II), heart rate, non-invasive arterial blood pressure, and pulse oximetry. The attending anesthesiologist managing intraoperative anesthesia was blinded to the patient grouping. At the end of surgery, all patients received bilateral nasal packs (Merocel-hydroxylated polyvinyl acetate, Medtronic Xomed, Jacksonville, FL, USA). Intravenous anesthetics were then discontinued, and after recovery of adequate spontaneous ventilation response, the patients were extubated and transferred to the post-anesthesia care unit (PACU). In the PACU, an acute pain nurse blinded to the patient grouping, recorded the degree of pain at time of admission and after 20, 40, and 60 minutes before discharge to the surgical ward. In case of inadequate pain relieve (VAS was ≥5 cm), rescue iv analgesia was given in 2 mg bolus doses of morphine sulfate (injected at 10 minutes intervals) until adequate pain relief was achieved (VAS <5 cm). Morphine consumption during the first hour after surgery was recorded. In the surgical ward, the pain was evaluated by surgical nursing staff (all surgical nursing staff are trained on the pain recording scale). The postoperative analgesia was in the form of lornoxicam 8 mg iv every 8 hours with rescue analgesia for VAS ≥5 cm in the form iv 1 gm paracetamol. The intensity of pain was recorded at 4, 8, 12, 18, and 24 hours after admission to the surgical ward and at time of pack removal. All nasal packs were removed on the second postoperative day after 24 hours from the surgery. Analgesia consumption and the VAS for each patient were reviewed by the blinded anesthesiologist and the surgeon, who knew the patient grouping, interpreted the results.

The statistical analyses were carried out using SPSS version 11.5 (SPSS, Inc., Chicago, IL, USA). Differences between the 2 groups were compared using independent t tests. The chi-square analysis was used for nominal data. The Mann-Whitney U test was used to look at the individual time points in order to evaluate for a difference between time points with regard to pain scores. A statistical significance was considered when the *p*-value <0.05.

Results. Eighty patients initially entered the study. Two patients from each group were excluded due to incomplete record for their pain level at specific time points (3 patients) and one patient was asked to stay outside the hospital due to psychological discomfort. The 2 groups were comparable regarding age, gender, weight, operative time, and operative procedures (**Table 1**). The difference in the duration of surgery between the 2 groups was insignificant (p=0.16). Pain score at PACU admission was significantly higher in the placebo group (mean 6.7 ± 14.5 SD) than for the DM group (mean 3.8 ± 16.4 SD), p=0.012 (**Figure 1**). Morphine consumption in the PACU was significantly higher in placebo group (mean 7.3 mg ± 2.6 SD) than for DM group (mean 4.6 mg ± 1.2 SD), p=0.03. Patients in the placebo group had higher pain score at 4, 8, 12, and 24 hours after admission to surgical ward than DM group but without statistical significance. Patients in the placebo group had a lower pain score at 18 hours, but this was insignificant (p=0.26) (**Figure 2**). Consumption of iv paracetamol in the surgical ward was statistically insignificant between both groups (mean 1.1 ± 2.2 gm for the placebo group, versus 1.05 ± 4.1 gm for the DM group, p=0.17). Pain score during pack removal was statistically higher (p=0.004) in the placebo group (mean 7.8 ± 11 SD) than the DM group (mean 3.5 ± 15 SD). There were no recognized drug side effects or surgical complications in either group.

Discussion. The degree of pain reported after FESS is usually of moderate intensity, nonetheless, routine use of local anesthetic infiltration or topical bupivacaine packing is usually not sufficient for the treatment of postoperative pain.[1] The results of this study suggest that preoperative administration of oral DM to patients undergoing nasal surgeries was associated with reduction of pain and consequently the amount of iv morphine sulfate at the admission to PACU compared with placebo. These results are compatible with those of Hasan et al,[11] and Dawson et al,[9] who demonstrated that preoperative administration of oral DM improved postoperative pain control and reduced total morphine consumption in children undergoing tympanomastoidectomies and adenotonsillectomies. However, Rose et al,[10] showed that there was no difference in postoperative pain control or analgesic administration between placebo and DM in children undergoing adenotonsillectomy. Opioids are traditionally used as a part of general anesthesia and for the treatment of acute post-operative pain. Recent research indicates that opioids produce not only analgesia, but also hyperalgesia, and consequently opioids may increase post-operative pain and opioid requirements[12,13] by enhancing NMDA receptor activation resulting in reduced potency of the opioid and opioid tolerance.[12] Although morphine is effective, it is also associated with frequent adverse effects such as sedation, nausea, vomiting, urinary retention, pruritus, and respiratory depression. For this reason, commonly used protocols of postoperative analgesia are based on

Table 1 - Anthropometric parameters of studied patients.

Parameters	DM group (n=38)	Placebo (n=38)
Age (years) (mean±SD)	28± 11	26 ± 10
Gender (M/F)	25/13	27/11
Surgery		
FESS	29	30
Septoplasty	5	5
FESS + septoplasty	4	3
Length of surgery in minutes	73.5 ± 22.1	77.3 ± 18.7

FESS - functional endoscopic sinus surgery

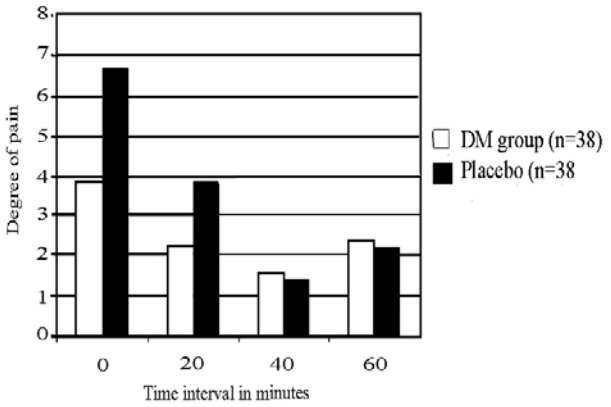

Figure 1 - Mean visual analog scale in the postanesthesia care unit. DM - dextromethorphan

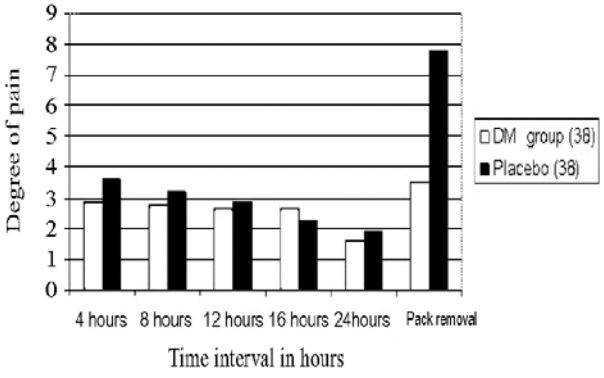

Figure 2 - Mean visual analog scale in the surgical ward. DM - dextromethorphan

a multi pharmacologic approach, which achieves a morphine sparing effect with concomitant reduction in morphine-related adverse effects.[14] Dextromethorphan is an isomer of the codeine analog levorphanol.[15] However, unlike codeine, its analgesic effects are mediated through noncompetitive antagonism of NMDA receptors. This results in a reduction in the glutamic acid, an excitatory amino acid in the CNS.[15] Glutamic acid is recognized to heighten pain perception following inflammatory stimuli.[3,15] Preoperative treatment with DM is believed to ameliorate the sensitization of the nociceptive neurons and thus facilitate postoperative pain management.[2] Dextromethorphan may also have weak analgesic and anti hyperalgesic properties.[2] In our study, we did not demonstrate any perceptible side effects related to DM. The safety of DM has been well established with the predominant side effects related to CNS stimulation only seen when large doses (>10mg/kg) were consumed.[16]

A VAS was chosen for pain scoring as it is deemed one of the most accurate and reproducible scales.[17] Although, such unidimensional scales cannot portray the complexity of pain records such as the MacGill questionnaire, which are hard to quantify and reproduce in surgical patients.[18] In our study, there was a maintained lower pain score, although insignificant, in the DM group at all time points in the surgical ward, except at 18 hours postoperative, which was also insignificant, indicating that the effect of DM could last beyond the perioperative period with extension to cover the whole postoperative admission period, and as expected, we observed that pain levels decreased with time in both placebo and DM groups. This was also seen in other reports. Gordon et al,[19] demonstrated the analgesic effect of large dose DM during the first 48 hour period in patients undergoing oral surgery, while, Aoki et al,[20] reported that it can be effective as long as 14 days after oral surgery under local anesthesia with lower consumption of analgesics than placebo using preemptive 30 mg oral DM. However, Hasan et al,[11] found that preoperative oral DM has no influence on pain control without analgesics beyond 8-10 hours after surgery. The explanation for such a finding is that DM is not used primarily as an analgesic but, instead, it was used to decrease the central nociceptive neurons sensitization and hence enhance the action of analgesics. In our study, we used lornoxicam as an analgesic for the postoperative period with preferable synergism between it and preemptive DM regarding pain level. It has been reported that the central sensitization may rarely occur during surgical procedures performed under local infiltrative anesthesia, because C fibers are blocked while tissue damage occurs, and a nociception-induced process diminishes in the secondary neurons. On the other hand, the administration of local anesthesia preoperatively did not produce any significant difference in pain levels compared with pain levels after general anesthesia alone.[21] There were many reports on reducing the pain of nasal packing after nasal surgeries using local analgesics (infiltration of the packs by lidocaine, bupivacaine) but the short-term effect ranged from 3-6 hours postoperatively without reduction of pain during the pack removal.[1,18,22-23] In our study, there was significantly lower pain score during pack removal than placebo. Reports on pain reduction during pack removal achieved comparable results using either pre-emptive Diflunisal (2 tablets 500 mg 90 minutes before pack removal,[24]) or pack rehydration with 0.25% tetracaine solution, 10 minutes before pack removal.[25] Laing and Clark[26] demonstrated, in a randomized trial that Entonox inhaled immediately prior to pack removal provided a statistically significant reduction in pain compared with intramuscular papaveretum or no analgesia. Although, these results are encouraging, it was related only to the event of pack removal unlike pre-emptive DM effects, which lowered the pain from the early postoperative period up to the pack removal time. Meanwhile, Lavy et al[27] compared removal of Merocel packs 10 minutes after one pack had been hydrated with lignocaine, and the other with saline, and interestingly, there was no statistical difference between packs, despite the expectation that lignocaine would have been at a therapeutic level after 10 minutes.

The limitation of this study includes nasal surgeries not being unique for all patients, as it depended upon the extent of pathology, and consequently the surgical trauma and postoperative pain may differ among the patients.

In conclusion, premedication with DM has a beneficial effect on postoperative pain following nasal surgery leading to reduction of opioid requirements in the first postoperative hour and has a marked pain reduction effect during removal of nasal packing. Further studies are needed to clarify the optimum dosage, timing, and frequency of DM administration preoperatively and if possible to continue its use postoperatively to maintain constant drug blood levels and consequently more beneficial effects.

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Related topics

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