Dextromethorphan attenuation of postoperative pain and primary and secondary thermal hyperalgesia

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Purpose: To determine the effect of 90 mg dextromethorphan (DM) *po vs* placebo 90 min preoperatively, on the immediate and delayed postoperative course.

Methods: Thirty patients undergoing laparoscopic cholecystectomy or inguinal hernioplasty under general anesthesia were studied. Half (DM) received 90 mg dextromethorphan and half received placebo 90 min before anesthesia. Intravenous Patient Controlled Aanalgesia with morphine was available for two hours within a six-hour observation period; 75 mg diclofenac *im prn* was given later in PACU and on-ward (24 hr). Pain was assessed using the visual analogue scales. Thermal thresholds for cold and hot sensation and for pain (by limit method) were evaluated at the site of skin incision (primary-) and distantly (secondary hyperalgesia). Von Frey filaments were applied testing touch sensation. Sedation level and morphine consumption were also assessed in PACU.

Results: Demographic, surgical and perioperative parameters were similar; no untoward effects were encountered. Pain intensity and sedation were lower, and the feeling of well-being was greater, in the DM patients: one *vs* five (median), two *vs* five, five *vs* two, respectively, $P < 0.01$ (90 min time-point). Thermal application revealed absence of primary and secondary hyperalgesia only in the DM patients; von Frey filaments induced similar pain sensation in both groups. Mean morphine/group, morphine/weight and diclofenac injection rates were ~55% lower in the DM group: 2.1 ± 1.2 (SD) *vs* 4.7 ± 2.3, 0.03 ± 0.02 *vs* 0.07 ± 0.03, 1.0 ± 0.3 *vs* 2.4 ± 0.2, respectively, $P < 0.01$.

Conclusions: Compared with placebo, DM enabled reduction of postoperative analgesics consumption, improved well-being, and reduced sedation, pain intensity and primary and secondary thermal hyperalgesia.

Objectif : Déterminer l'effet de 90 mg de dextrométhorphane (DM) *po vs* un placebo, administrés 90 min avant l'opération, sur l'évolution postopératoire immédiate et tardive.

Méthode : L'étude a porté sur 30 patients devant subir une cholécystectomie laparoscopique ou un hernioplastie inguinale. La moitié a reçu 90 mg de dextrométhorphane et l'autre moitié, un placebo, 90 min avant le début de l'anesthésie générale. La morphine, en qualité d'analgésie intraveineuse autocontrôlée, a été disponible pendant deux heures sur une période d'observation de six heures; 75 mg de diclofénac *im prn* ont été administrés plus tard à la salle de réveil et à la chambre (24 h). La douleur a été évalué grâce à l'échelle visuelle analogique. Les seuils thermiques de sensation au froid et à la chaleur ainsi qu'à la douleur (selon une méthode du seuil différentiel) ont été évalués au site de l'incision cutanée (hyperalgésie primaire) et à distance (hyperalgésie secondaire). Des filaments von Frey ont été appliqués pour tester le toucher. On a aussi évalué, à la salle de réveil, le niveau de sédation et la consommation de morphine.

Résultats : Les paramètres démographiques, chirurgicaux et périopératoires ont été similaires; aucun effet indésirable n'a été noté. L'intensité de la douleur et de la sédation a été plus faible, et le confort meilleur, chez les patients du groupe DM : un *vs* cinq (médiane), deux *vs* cinq, cinq *vs* deux, respectivement, $P < 0{,}01$ (90 min après le début de l'analgésie). L'épreuve de sensibilité thermique a révélé l'absence d'hyperalgésie primaire et secondaire chez les patients du groupe DM seulement; les filaments von Frey ont induit une sensation de douleur similaire chez les patients des deux groupes. La consommation moyenne de morphine selon le groupe et selon le poids des patients ainsi que les taux d'injection de diclofénac ont été de ~55 % plus bas dans le groupe DM: 2,1 ± 1,2 (écart type) *vs* 4,7 ± 2,3; 0,03 ± 0,02 *vs* 0,07 ± 0,03; 1,0 ± 0,3 *vs* 2,4 ± 0,2, respectivement, $P < 0{,}01$.

Conclusion : Comparé à un placebo, le DM a permis de réduire la consommation d'analgésiques postopératoires, a amélioré le confort et a réduit la sédation, l'intensité de la douleur et l'hyperalgésie thermique primaire et secondaire.

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THE involvement of *N*-methyl-D-aspartate (NMDA) receptors in modulating the process of central sensitization and perception of pain is well-established.[1] The process of the arrival of pain stimuli from the periphery, and the role of these receptors, mediated by excitatory amino acids, in causing perpetuation and aggravation *vs* modulation of acute and chronic pain have been comprehensibly described as well.[2–4] Dextromethorphan (DM), the D-isomer of the codeine analog levorphanol of established clinical safety,[5] is an NMDA receptor antagonist which, when administered before a nociceptive stimulus is applied, reduced slow temporal summation of electrically and thermally evoked secondary pain sensation in a dose-dependent manner.[6] Both A and C fibres are involved in the transmission of both thermal and pain sensation towards the cortex.[7] Thus, heat and cold stimuli could determine more precisely and objectively perception of pain that is evoked and transmitted via these fibres, before and after drug application.[8]

We investigated the effect of oral DM premedication during a six-hour postoperative period on pain intensity perception, morphine requirement, and patients' subjective ratings of parameters, such as changes in the thermal threshold and pressure-touch sensation.

Patients and methods

Study groups

Thirty patients (ASA I-III) undergoing laparoscopic cholecystectomy or inguinal hernioplasty under general anesthesia were enrolled in this prospective, double blind study. After institutional human research and ethics committee approval, patients gave written informed consent to participate and received a full explanation regarding DM, the intravenous patient controlled analgesia (*iv*-PCA) device and the mode of administration of morphine (MO), and the linear visual analogue scale (VAS) mode of evaluation on the day before surgery. They were trained to use the Thermal Sensory Analyzer (see below). Half of the patients were given oral 90 mg DM 90 min before the operation and the rest received placebo. Baseline cardiovascular and respiratory vital signs were recorded; no other drugs were administered preoperatively.

Exclusion criteria were treatment by the use of opioids of any sort, non-steroidal anti-inflammatory drugs (NSAIDs), sedatives, centrally acting antihypertensive drugs, CNS depressants or antidepressants during the 21 dy before the study. Patients aged < 18 yr, pregnant women and individuals suffering from congenital or acquired neuromuscular disease or chronic pain were also excluded.

Anesthesia and surgery protocols

Anesthesia was induced with 4 $mg \cdot kg^{-1}$ thiopental and endotracheal intubation was facilitated with 1.5 $mg \cdot kg^{-1}$ succinylcholine. Anesthesia was maintained with a 50% mixture of oxygen and nitrous oxide (N_2O) fresh gas flow. Atracurium was infused as necessary and 2.5 $\mu g \cdot kg^{-1}$ fentanyl was used for maintaining anesthesia. At the end of surgery, N_2O was stopped and neuromuscular relaxation was not reversed pharmacologically. Based on normal train-of-four and clinical criteria, the trachea was extubated and patient was taken to the Post Anesthesia Care Unit (PACU).

Patient assessment

Vital signs were recorded upon arrival to the pre-anesthesia area. Differences of >20% compared with earlier baseline values excluded the patient from the study.

In the PACU, the patients were under close observation of a physician. When the patient complained of pain intensity 4 on the subjective 0-10 pain VAS (see below), an *iv*-PCA system was activated by the anesthesiologist who was blinded to the patient's group assignment. A bolus of 2 mg morphine was administered by the attending physician and this was followed by 1-mg boluses at the patient's request. Lockout time was set at seven minutes. *iv*-PCA was administered for two hours, after which patients remained in the PACU for observation for a total study period of six hours in order to assure the recognition of late-onset pain or sedation.

The following parameters were assessed in each patient:

1. Thermal sensation: This test evaluated patient-determined changes in heat and cold sensation and pain thresholds. Baseline tests were performed 30 min before drug premedication, and postoperative values were obtained 30 min after the patient's arrival to the PACU and when sedation score as judged by the attending anesthesiologist was 3 (see below). The test was performed again 60 min later and the resulting mean of the postoperative tests is reported as one value. This average was considered appropriate since it tested the effect of DM rather than the cumulative effect of MO over time.

Changes in the thermal thresholds were evaluated using the 2001 Thermal Sensory Analyzer (TSA)™ (MEDOC®, Ramat Yishai, Israel) that applied the methods of limits.[9] This method is less time consuming and more suitable to postoperative patients than the methods of levels,[10] and is consistent in detecting changes of thermal sensation in a sequential recording.[11] This methodology allows a dermatome-related evaluation of subjective warmth and cold threshold

sensations and of when a sensation of warmth becomes painfully hot as well as when mere cold reaches a level of inducing pain whereupon the patient halts the stimulus.[10] The device delivers stimuli of increased intensity starting at skin temperature, the rate of which changes was set to 1°C/1.5 sec and room temperature was kept stable at 25°C. The temperature of the stimulus then immediately returned to adaptation temperature, in preparation for the next stimulus. Several successive stimuli are given at the same skin area, and the thresholds are recorded in order to derive the mean threshold. Four stimuli are usually sufficient for threshold temperature determination. The tests were performed bilaterally at the midaxillary line at T_{10} (within the area immediately adjacent to the site of skin incision and laparoscope insertion, the "primary hyperalgesic zone") and at the level of T_6 (~10 cm cephalically to the site of incision, the "secondary hyperalgesic zone"). The mean of each bilateral value was considered as one result.

2. Von Frey filaments: This skin touch and pain meter was applied bilaterally as noted above. Patients were asked to close their eyes and the von Frey hairs, starting with No. 1, were applied to the area to be tested. Each hair was applied once to the site and the patient was asked to report its sensation and recognition of the touch, the "touch threshold". Thresholds of pain were determined at the same sites. The patient was then asked to open his/her eyes and to report when the sensation elicited by the filaments first became painful. This double-checking was intended to exclude the possibility that the patient indicated pain before having sensed the touch of the filament. This evaluation was applied 30 min after TSA application to avoid interdependent response. Due to technical reasons, both TSA and von Frey measurements were not continued on the ward.

3. Subjective pain intensity: Patients used a linear VAS from 0 (no pain) to 10 (unbearable pain).

4. Objective sedation (judged by the attending anesthesiologist): 1=awake and tense, 2=awake and calm, 3=drowsy and calm, 4=drowsy with frequent awakening due to pain, 5=sedated and calm, 6=sedated but wakes up to a state of drowsiness associated with pain.

5. Subjective sedation: Based on VAS 1-10 (fully awake - heavily sedated);

6. Subjective feeling: Based on VAS 1-10 (sad, gloomy - happy, content).

7. Total morphine consumption: The individual and mean group-consumed MO were assessed at the end of the experiment.

8. Number of requests: Due to the lockout time, the number of requests for morphine boluses by the *iv*-PCA button pressure was noted separately.

The monitored vital signs included heart rate, systolic and diastolic non-invasive blood pressures, respiratory rate, end-expired CO_2, SpO_2 (Cardiocap™, Datex-Ohmeda®, Helsinki, Finland) and a 5-lead ECG. Side effects that would have occurred were recorded by the protocol-blinded attending physician and treated accordingly.

At the end of the six-hour study period, the patients were transferred back to the ward in accordance with the PACU discharge regulations; they were all sent home 24 hr later. A late on-the-ward follow-up recorded patients' pain VAS and the number of times diclofenac 75 mg intramuscularly was administered, as well as the rate of PONV.

Statistical analysis

The analyses were performed at the Statistical Laboratory of the Tel-Aviv University using the BMDP Statistical Software (W. J. Dixon, Chief Editor, University of California Press, USA, 1992) and the SPSS Release for IRIS, Version 9 (USA, 1999). The background characteristics of the two study groups were compared using the t test. ANOVA or co-ANOVA with repeated measures was used to evaluate differences between the two study groups, changes over time during treatment and time-treatment interactions where appropriate. Paired t tests were used to assess the initial effect of treatment by comparing values prior to the first bolus (loading dose) to those immediately afterwards. Fisher's exact test was used to compare categorical variables. Since various VAS scores, both objective and subjective, could also be regarded as being non-parametric, they were analysed using the Mann-Whitney U – Wilcoxon Rank Sum Test. Thermal thresholds and pain sensations as well as von Frey thresholds were analysed with the Mann-Whitney U test. The effect of DM on pain expressed by the need for MO and number of button presses were analysed with the non-parametric Freedman ANOVA. All parametric values are expressed as mean ± standard deviation (SD) and the non-parametric by median and ranges, with significance defined as P 0.05.

Results

There were no differences between the two study groups in terms of age, weight, ASA grade, the type and the duration of surgery (Table I). Two patients from each group were withdrawn from the study because of failure to maintain proper respiration following extubation or due to failure to report the use of benzodiazepine in advance. None of the patients

TABLE I Patients data (mean ± SD).

	DM90	*Placebo*	*P*
Age (yr)	35 ± 1	35 ± 3	NS
Sex (male / female)	8 / 5	9 / 4	NS
Weight (kg)	70 ± 7	67 ± 8	NS
ASA	1.9 ± 0.5	1.7 ± 0.2	NS
Cholecystectomy / inguinal hernioplasty	8 / 5	6 / 7	NS
Duration of surgery (min)	85 ± 9	94 ± 12	NS
Button pressed (*n X*)	3.1 ± 0.3	8.6 ± 1	0.001
Morphine (mg)	2.1 ± 1.2	4.7 ± 2.3	0.01
Morphine / body weight ($mg \cdot kg^{-1}$)	0.03 ± 0.02	0.07 ± 0.03	0.01
On-ward subjective pain VAS	1.2 ± 0.5	2.3 ± 0.4	0.01
On-ward use of diclofenac (*nX*)	1.0 ± 0.3	2.4 ± 0.2	0.001

DM90=90 mg oral dextromethorphan, ASA=American Society of Anesthesiologists class; *n X*=number of times used; NS=not significant.

TABLE II Thermal cold and heat and pain threshold sensations (expressed in C) and pressure-touch-induced pain threshold (expressed by numerical scale) data (mean ± SD).

Site	*Test*	*DM90 patients*		*Placebo patients*		
		Preop	*Postop*	*Preop*	*Postop*	*P*
T_{10}	Heat sensation threshold	35.6 ± 1.6	36.5 ± 1.6	35.6 ± 0.9	35.1 ± 1.0	0.01
	Cold sensation threshold	30.0 ± 1.0	28.0 ± 1.7	27.7 ± 2.0	29.3 ± 1.5	0.03
	Heat pain sensation threshold	40.2 ± 1.3	42.5 ± 1.8	42.6 ± 2.9	40.9 ± 2.3	0.04
	Cold pain sensation threshold	26.5 ± 2.0	20.1 ± 5.0	22.7 ± 6.0	25.2 ± 4.9	0.01
T_6	Heat sensation threshold	34.6 ± 0.7	35.9 ± 1.3	35.5 ± 1.0	35.4 ± 1.9	NS
	Cold sensation threshold	31.2 ± 0.9	28.6 ± 2.1	27.8 ± 2.2	29.1 ± 2.0	NS
	Heat pain sensation threshold	39.01 ± 1.4	41.3 ± 2.5	40.9 ± 2.3	40.9 ± 2.1	NS
	Cold pain sensation threshold	26.1 ± 2.7	21.4 ± 5.7	22.7 ± 3.5	25.8 ± 3.6	0.02
T_{10}	Von Frey pain sensation	2.64 ± 0.74	4.28 ± 1.20	3.53 ± 2.14	3.76 ± 1.53	NS
T_6	Von Frey pain sensation	1.85 ± 0.66	4.14 ± 1.95	3.00 ± 1.95	3.23 ± 1.57	NS

DM90 =90 mg oral dextromethorphan; Preop=preoperatively; Postop=postoperatively.

**P* values apply to differences between the preoperative and postoperative values in the placebo patients or between the pre- and postoperative differences in the placebo compared to the differences in the DM90 patients.

was excluded form the study because of perioperative changes >20% in vital signs.

Morphine consumption, pain and sedation scores

Both the total postoperative self-administered MO consumption and the MO requirement per body weight during the two-hour *iv*-PCA period were (P <0.01) lower in the DM-treated than in the placebo-administered patients, as was the number of times the button was pressed (Table I), but not the number of patients who did not request MO at all (1 *vs* 0). The cumulative doses of MO used by the two groups at the time of the thermal and the von Frey measurements were similar (data not shown). None of the DM patients requested diclofenac in the PACU, two placebo-injected individuals (P <0.05) made use of one dose each.

Subjectively, evaluated pain intensity by VAS demonstrated that pain soon after surgery was at or above the predetermined (4 / 10) score in most patients (Mann Whitney U test). Differences between the groups were detected at all times starting 30 min after the *iv*-PCA was started (Figure, upper plane). The subjectively assessed feeling was similar between the groups during the first part of the study but the DM patients rated their feeling (P <0.01) better than the placebo individuals (Figure, central plane) towards the end. Both subjective and objective sedation ratings indicated deeper sedation in the placebo group than in the DM group (P <0.01) throughout the study (Figure, lower plane).

Thermal and touch threshold determinations

Changes in the cold and heat thermal sensation thresholds measured bilaterally at the T_{10} levels in the DM-treated patients remained either unchanged from baseline or there was a newly generated resistance to temperature tests, i.e., patients perceived less heat or

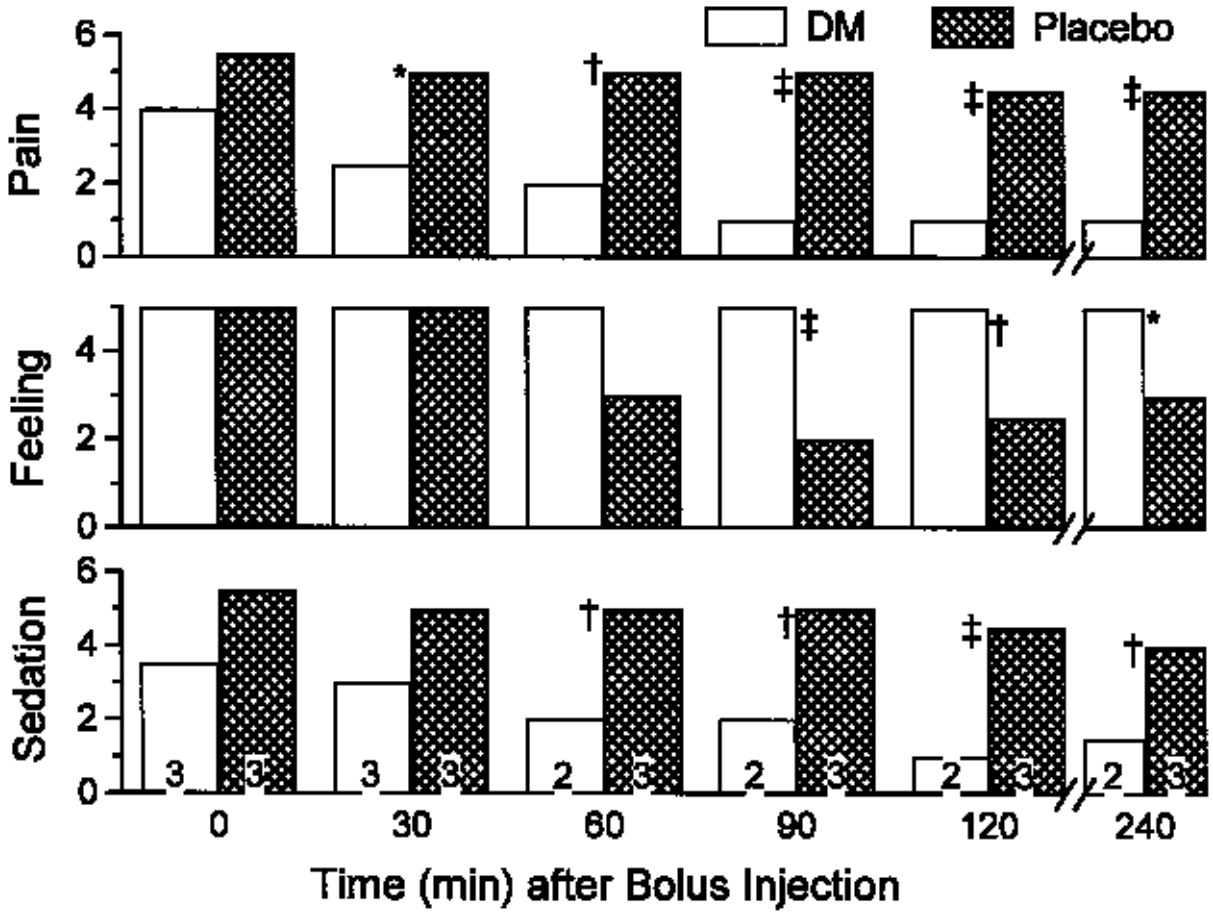

FIGURE Subjective patient data (expressed as medians).
Pain depicts patient's self judgment of pain intensity on a 0-10 (none-unbearable) linear visual analogue scale (VAS); feeling depicts patient's subjective 1-10 (worst-best) VAS of well-being; sedation is patient's own description on a 1-10 (awake-sedated) VAS. Numbers within the columns represent anesthesiologist's judgment of patient's sedation on a 1-6 (awake-sedated) scale.
*P <0.05, †P <0.01, ‡P <0.001 between the dextromethorphan (DM)-treated and the placebo-administered patients.

cold sensation and were better resistant to warm- and cold-induced pain. The placebo-administered patients had reduced thresholds so that they sensed cold at higher temperatures and heat at lower grades than before drug administration and surgery, compared with DM patients (Table II). This indicated that the placebo patients experienced primary thermal hyperalgesia and hyperpathia at sites near the site of surgery. At a site distant to the injured dermatome (T_6), this phenomenon reiterated for cold pain sensation threshold, where DM patients sensed pain at grades lower than before, while the placebo group sensed temperature more acutely and in the opposite direction; only the difference in cold pain thresholds reached statistical significance between the groups (Table II). Heat sensation and pain thresholds did not delineate statistical differences between the groups.

Von Frey filaments detected slight changes in skin sensitivity (data not shown). Skin touch-induced pain both at the site near the cut wound (T_{10}) and at the more cephalically (T_6) site in the DM group, but these did not reach a statistical difference compared to the changes in the placebo group (Mann-Whitney T test, Table II).

Postoperative follow-up: the three- to six-hour PACU phase

All patients were disconnected from the *iv*-PCA without incident and none required supplementary MO during this period. All the tested parameters were con-

tinually assessed and showed no change from the two-hour evaluation phase (data not shown). None of the patients suffered from untoward somatic, visceral or behavioural symptoms throughout surgery and the study period. They were all discharged uneventfully according to PACU regulations.

Vital signs

Vital signs changed slightly as expected in patients undergoing surgery under general anesthesia, but all were within 10-12% of baseline values (data not shown).

Postoperative follow-up: the ward phase

None of the patients suffered from untoward effects in the 24- hr after surgery, including PONV. The mean pain VAS and the number of times patients in each group received 75 mg diclofenac *im* were (P <0.05) lower in the DM group than in the placebo group (Table I). Four DM patients *vs* no placebo patients (P <0.05) did not make any use of diclofenac.

Discussion

These results demonstrated the effectiveness of oral premedication with DM 90 mg in patients requiring cholecystectomy and hernioplasty via laparoscopic surgery under general anesthesia. In addition to lowering *iv*-PCA MO and diclofenac requirement, DM reduced postoperative primary and secondary hyperalgesia and hyperpathia. This is the neuropharmacological basis for which DM-treated patients rated their pain as being less both immediately and 24 hr after surgery. Their subjective sedation and feelings scores were also better than those of the placebo group. The lack of side effects taken together with the herein presented DM antinociceptive capability and the abolition of primary and secondary heat and cold hyperalgesia seems to bestow upon DM an important place among perioperatively used drugs.

Dextromethorphan influences peripheral pain transmission at the level of the NMDA spinal receptors.[12-14] Its ability to suppress the NMDA receptors-induced "wind up" or central hypersensitization is the basis for its antinociceptive use.[4,15] The pro-analgesic capabilities of DM both when used alone in volunteers and as an analgesic adjuvant in clinical setting still lack unequivocal details.[15] For example, Chia *et al*. showed that a single dose of 5 $mg \cdot kg^{-1}$ intravenous DM premedication in patients who underwent intra-abdominal surgery under isoflurane / fentanyl / N_2O-based general anesthesia was effective in reducing postoperative pain sensation and diclofenac requirement for the two study days.[16] Hendersen and colleagues treated patients undergoing hysterectomy under enflurane-enriched 70% N_2O-based general anesthesia with 40 mg DM preoperatively and *tid* the day after surgery with beneficial results.[17] On the contrary, DM at doses of 0.5 or 1.0 $mg \cdot kg^{-1}$ did not reduce pain score, analgesic requirement or other subjective and objective scores in children after tonsillectomy under multi-drug general anesthesia during the 24-postoperative hr.[18] Also, Grace *et al*. demonstrated that 60 mg DM given the night before surgery to non-premedicated patients scheduled for laparotomy under isoflurane + morphine + N_2O-based general anesthesia reduced the intraoperative morphine requirement based on blood pressure and heart rate, but not the postoperative patient-controlled morphine requirement.[19] These and other contrasting and equivocal data dictated the present restricted drug protocol of no premedication except for the DM, N_2O 50% in oxygen and medium-dose intraoperative fentanyl to maintain anesthesia. Only MO by *iv*-PCA device was administered in the immediate postoperative period and only diclofenac during the later 24 hr so that the subjective and objective assessments could be more accurate and reliable.

The present study evaluated the level of sedation, a rarely used parameter in previous studies. Sedation is one of the paramount yardsticks in the postoperative period because of its linkage to the possible occurrence of respiratory and hemodynamic complications, particularly in the presence of general anesthetic residue. The objective and the subjective evaluations of the patient's reduced sedation after DM attest to a high safety record of DM.

Receptive fields of dorsal horn neurones in animals were shown to change after peripheral inflammation[20] with a subsequent increased state of excitability which may persist long after afferent C-fibre activity has ceased.[21,22] Clinically, this manifests as thermal or mechanical allodynia at sites both proximal to and distant from the inflamed area, i.e., primary and secondary hyperalgesia, respectively, and hyperpathia, which also includes conditions of hyperalgesia (i. e., pain sensation in response to a stimulus that may or may not cause pain). We hypothesized that this phenomenon could occur postoperatively, and therefore applied both non-painful and painful thermal stimuli that are characteristically conveyed by the same peripheral fibres used for transmission of peripheral pain.[8] Only one study of eight volunteers used thermal threshold and pain sensation to test the effect of oral 100 mg DM *po* on post injury pain intensity but the result was inconclusive.[23] Our placebo-administered patients displayed a primary heat and cold-induced hyperalgesia and secondary cold-induced pain thresh-

old, while DM treatment was associated with resistance to these stimuli, i.e., they did not develop thermal-induced hyperalgesia and hyperpathia. Combining these results with the findings that DM patients also used fewer analgesics and had lower pain intensity, it can be concluded that 90 mg DM *po* 90 min preoperatively attenuates pain that is generated at the site of injury and is conveyed via C and A fibres during general anesthesia. It also annulled the state of "windup" that is associated with tissue injury, thus minimizing primary and secondary hyperalgesia.

The reason for the contrasting results between the positive thermal sensation test and the negative von Frey filaments test may lie in their distinct potentials of pain generation, although the von Frey test neither detected differences in hyperalgesia between DM and placebo patients in a recent post surgery study.[24] Additionally, in one of the first studies on preemptive analgesia[25] where pressure hyperalgesia was evaluated, it appeared that this test might be an inappropriate tool because it generates a light, sometimes non-perceivable stimulus to generate specific central perception of pressure hyperalgesia. In such cases, DM might not exert an identifiable clinical effect of post-injury hyperalgesia compared to placebo.

No side effects were recorded in the current study, in contrast to reported high rates, especially where DM was administered parenterally.[16] We explain this by the DM low bioavailability and thus low plasma levels that follow oral administration compared to the much higher levels after a parenteral one.[26] The lack of side effects is a promising fact especially insofar as no pain exacerbation[21] and post general anesthesia nausea / vomiting ever occurred in our patients.

In conclusion, DM was effective in sparing postoperative analgesics up to 24 hr, reducing pain intensity, and improving patients' feeling and lowering their sedation rating after general anesthesia. DM was also capable of abolishing post-surgery thermal-induced hyperalgesia and hyperpathia. A better understanding of the intricate mechanisms of interaction between DM, the NMDA receptor and possibly other factors that converge positively or negatively on NMDA receptor modulation of acute pain would probably pave the way for greater recognition of the value of DM.

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