Preincisional dextromethorphan decreases postoperative pain and opioid requirement after modified radical mastectomy

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Purpose: To examine whether preincisional dextromethorphan (DM) improved analgesia after modified radical mastectomy (MRM).

Methods: Sixty patients (ASA I-II) scheduled for MRM were included and randomly allocated into two groups. Patients in the treatment group (DM) received 40 mg DM and 20 mg chlorpheniramine maleate (CPM) *im*, and those in the control group received 20 mg CPM *im* alone 30 min before skin incision. Meperidine, 1 $mg \cdot kg^{-1}$ *im*, was given for postoperative pain relief as required. The time to first meperidine injection, total meperidine consumption, worst pain score, bed-rest time, and side effects were recorded every 24 hr for 48 hr after surgery by a resident anesthesiologist on a double-blind basis.

Results: A longer time to first meperidine injection (19.2 ± 1.6 *vs* 1.5 ± 0.23 hr, $P < 0.001$) and lower meperidine consumption (0[10] *vs* 75[50] mg, median [interquartile range], $P < 0.001$) were observed in the DM group than in the control group. The bed-rest time was shorter in the DM than in the control group (18.0[4] *vs* 23.0[19] hr, $P < 0.001$). No difference was noted in worst VAS pain score. Meperidine-related side effects (nausea, vomiting, pruritus, dizziness, headache) were more frequent in the control (10/30) than in the DM group (3/30, $P < 0.05$). The number of patients who required meperidine injection for pain relief was lower in the DM (7/30) than in the control group (25/30, $P < 0.005$). No DM- or CPM-associated side effects were observed.

Conclusion: Preincisional IM. DM treatment decreased postoperative pain and opioid requirement after MRM surgery.

Objectif : Déterminer si l'administration préincision de dextrométhorphane (DM) améliore l'analgésie à la suite d'une mastectomie radicale modifiée (MRM).

Méthode : Soixante patientes (ASA I-II) qui devaient subir une MRM ont participé à l'étude et ont été réparties au hasard en deux groupes. Les patientes du groupe de traitement (DM) ont reçu 40 mg de DM et 20 mg de maléate de chlorphéniramine (MCP) *im*, et celles du groupe témoin ont reçu 20 mg de MCP *im* seulement, 30 min avant l'incision cutanée. De la mépéridine, 1 $mg \cdot kg^{-1}$ *im*, a été administrée sur demande après l'opération pour soulager la douleur. Ont été enregistrés par un anesthésiologiste en service selon un mode à double insu : le temps écoulé avant la première injection de mépéridine, la consommation totale de mépéridine, la douleur la plus intense, le temps de repos au lit et les effets secondaires.

Résultats : Un délai plus long avant la première injection de mépéridine (19,2 ± 1,6 *vs* 1,5 ± 0,23 h, $P < 0,001$) et une plus faible consommation de mépéridine (0[10] *vs* 75[50] mg, médiane [étendue interquartile], $P < 0,001$) ont été observés dans le groupe DM comparé au groupe témoin. Le temps de repos au lit a été plus court dans le groupe DM que dans le groupe témoin (18,0[4] *vs* 23,0[19] h, $P < 0,001$). Aucune différence n'a toutefois été notée quant à la douleur la plus intense selon l'EVA. Les effets secondaires reliés à la mépéridine (nausées, vomissements, prurit, étourdissements, céphalées) ont été plus fréquents dans le groupe témoin (10/30) que dans le groupe DM (3/30, $P < 0,05$). Moins de patientes du groupe DM (7/30) que du groupe témoin (25/30) ont demandé une injection de mépéridine pour soulager la douleur, $P < 0,005$). On n'a pas observé d'effets secondaires associés au DM ou au MCP.

Conclusion : L'administration préincision et intramusculaire de dextrométhorphane a réduit la douleur et les besoins d'opioïdes postopératoires à la suite d'une mastectomie radicale modifiée.

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MODIFIED radical mastectomy (MRM) is one of the most common surgical procedures performed in Taiwan for breast cancer patients. Postoperative pain and discomfort often accompany this procedure, so that satisfactory postoperative analgesia is desirable. Dextromethorphan (DM), an antitussive drug, has been used for over 40 yr with a wide margin of safety.[1] Both DM and its metabolite dextrorphan have non-competitive NMDA antagonist properties.[2-4] Dextromethorphan reduces spinal nociceptive neuron hyperexcitability.[5] Previously, we demonstrated that preincisional treatment with the NMDA antagonist, ketamine, improved postoperative analgesia after surgical incision for total knee replacement.[6] This lead to renewed interest in DM for clinical pain management.[7-15] Kawamata *et al.* reported that premedication with DM may prevent NMDA receptor-activated central nociceptor sensitization and reduce postoperative pain after tonsillectomy.[7] More recently, we demonstrated that preincisional *im* DM treatment decreased postoperative pain after upper abdominal surgery.[8] In the present study, we evaluated whether preincisional DM treatment improved postoperative pain management after MRM surgery.

Methods

This study was approved by the Protection of Human Subjects Institutional Review Board of Tri-Service General Hospital. Written informed consents from all patients were obtained before inclusion in the study. Patients who received opioids or non-steroidal anti-inflammatory drugs (NSAIDs) within one week before surgery were excluded from the study. Patients taking medications that could interact with dextromethorphan, including quinidine, flecainide, mexiletine, fluoxetine, amitriptyline, nortriptyline, and propafenone were also excluded. Sixty patients (ASA I-II) undergoing MRM were selected for a randomized, double-blind trial and allocated into two groups. After induction of general anesthesia, patients in the treatment group (n=30) received 40 mg DM and 20 mg chlorpheniramine maleate (CPM) *im*, as a part of the domestic injected form of antitussive, 30 min before skin incision. Those in the control group (n=30) received 20 mg CPM *im* alone 30 min before skin incision. The available injection form of one ampule DM (10 mg) contains 5 mg CPM. Therefore, 20 mg CPM were given to the control group to rule out the effect of CPM treatment.

General anesthesia was induced with 2 $\mu g \cdot kg^{-1}$ fentanyl, 5 mg atracurium, 3-5 $mg \cdot kg^{-1}$ thiopental and 1.5 $mg \cdot kg^{-1}$ lidocaine, and tracheal intubation was facilitated with 1.5 $mg \cdot kg^{-1}$ succinylcholine. Anesthesia was maintained with desflurane in oxygen (300 $ml \cdot min^{-1}$) with a total closed-circuit system; the end-tidal desflurane concentration was maintained around 6.5 ± 0.5%. Atracurium was used for muscle relaxation. No additional opioids were given during the operation. Standard monitors included pulse oximeter, ECG, NIBP, and capnography were prescribed during the operation. At the end of surgery, residual neuromuscular block was antagonized with 0.8 $mg \cdot kg^{-1}$ edrophonium and 0.01 $mg \cdot kg^{-1}$ atropine, and the endotracheal tube was removed when the patient breathed spontaneously. After surgery, patients stayed in the post-anesthesia recovery room for two hours. During this period, DM and CPM-associated side effects (such as dizziness, hot flushes, tremor, drowsiness, heartburn, nausea, and vomiting) were recorded. All patients were made familiar with the visual analog scale (VAS; 0= no pain, 10= the worst pain imaginable) on the day before surgery. Patients received 1 $mg \cdot kg^{-1}$ meperidine *im* for postoperative pain relief, if required. We recorded the time to first meperidine injection, the worst pain scores, total meperidine consumption, meperidine-related side effects (nausea, vomiting, pruritus, dizziness, and headache) and bed-rest time every 24 hr for 48 hr after operation. A resident anesthesiologist did all the assessments on a double-blind basis. Side effects were treated with medications, if necessary.

Most data are presented as mean ± SEM. Demographic characteristics were compared between groups using Student's t tests. During the 48 hr follow up after surgery, some patients did not receive meperidine; the log-rank test was used to evaluate the difference of the time to first meperidine injection. Total morphine consumption, bed-rest time and worst pain scores were compared using the Mann-Whitney *U* test for variables they were not normally distributed. The Chi-square test was used to evaluate the distributions of meperidine requirement and related side effects between groups. A P value <0.05 was considered as statistical significant.

Results

There were no differences in demographics or surgical time between the two groups (Table I). The median time to first meperidine injection was longer in the DM group (19.2 ± 1.6 hr) than in the control group (1.5 ± 0.23 hr, $P < 0.001$) (Table II). Higher total meperidine consumption was observed in the control group (75[50] mg, median [interquartile range]) than in the DM group (0[10] mg, median [interquartile range] $P < 0.001$) during the 48 hr follow-up after surgery

TABLE I Demographic characteristics and surgical duration of subjects.

	DM (n=30)	*Control (n=30)*
Age (yr)	53.8 ± 2.2	51.4 ± 2.7
Weight (kg)	57.5 ± 1.8	59.5 ± 1.7
Height (cm)	154.5 ± 1.1	157.4 ± 1.2
Surgical duration (hr)	2.8 ± 0.2	2.7 ± 0.2

Mean ± SEM.

TABLE II Postoperative analgesia, bed-rest time, meperidine requirement and related side effects.

	DM	*Control*	*P*
Time to 1st meperidine injection (hr)*	19.2 ± 1.6	1.5 ± 0.23	<0.001
Total meperidine consumption (mg)†	0[10]	75[50]	<0.001
Bed-rest time (hr)†	18[4]	23[19]	<0.001
Meperidine requirement‡	7/30	25/30	<0.005
Meperidine-related side effect‡	3/30	10/30	<0.05

* Log-rank test. Median ± SEM was used in the control group. In the DM group, only seven of 30 patients used meperidine within 48 hr after surgery, no median value can be calculated, thus, mean ± SEM was used instead.

† Mann-Whitney U test. Data are presented as median and interquartile range.

‡ Chi-square test.

TABLE III Visual Analog Pain Scores (VAS).

	DM (n=7)	*Control (n=25)*	*P*
At first meperidine injection	6.0 ± 0.2	6.3 ± 0.2	0.44

Mean ± SEM.

(Table II). In addition, the average bed-rest time was shorter in the DM group (18[4] hr) than in the control group (23[19] hr, median [interquartile range] $P < 0.001$). No differences were sen in the worst pain score between the control group (6.3 ± 0.2) and the DM group (6.0 ± 0.2, P=0.44). The worst pain score were reported at the time of meperidine injection, particularly the first meperidine injection (Table III). However, there was a reduction in the number of patients who required meperidine within 48 hr in the DM group (7/30) than in the control group (25/30, $P < 0.005$) (Table II). Meperidine-associated side effects (such as nausea, vomiting, pruritus, dizziness and headache) were observed at a higher frequency in the control group (10/30) than in the DM group (3/30, $P < 0.05$) (Table II). The VAS score was < 3 in those patients who did not request meperidine for pain relief in both groups. No DM or CPM-associated side effects (such as dizziness, hot flushes, tremor, drowsiness, heartburn, nausea, and vomiting) were observed within the two hours observation in post-anesthesia recovery room (data not shown).

Discussion

The present study showed that preincisional *im* DM improved postoperative pain relief after mastectomy. Dextromethorphan produced a longer time to first meperidine injection, lower total meperidine consumption, and shorter bed-rest time. Furthermore, a reduction in the number of patients who required meperidine for pain relief and meperidine-related side effects were also observed in the DM group. These results were consistent with our previous work that *im* DM (40 mg) prior to surgical incision provided better postoperative pain relief, in a dose-dependent manner, after upper abdominal surgery.[8]

In animal studies, DM and its metabolite dextrorphan attenuate temporal summation of nociceptive signals in the spinal dorsal horn neurons,[2] suppress formalin-induced nociceptive behaviour and *c-fos* mRNA expression in rat spinal cord,[4] and reduce neuropathic pain syndromes.[16,17] Similar results have been observed in human studies.[7–10] Price *et al.* found that DM reduced slow temporal summation of electrical- and thermal-evoked second pain and in a dose-dependent manner.[9] Ilkjer *et al.* demonstrated that DM reduced the magnitude of secondary hyperalgesia to pinprick and prolonged noxious heat stimulation.[10] Recently, Kawamata *et al.* also reported that premedication with 45 but not 30 mg DM *po*, reduced postoperative pain after bilateral tonsillectomy.[7] The present finding was consistent with the results mentioned above; preincisional DM treatment provided satisfactory postoperative pain relief.

In contrast, some controversial results have been reported.[11–15] McQuay *et al.* failed to demonstrate an analgesic effect of DM on neuropathic pain syndromes using oral doses of 40.5 mg or 81 mg daily for a 10 day observation period.[11] Grace *et al.* found that preoperative oral DM (60 mg) did not improve post-laparotomy analgesia.[12] McConaghy *et al.* reported that DM pretreatment (54 mg, *po*) did not offer any benefit for postoperative pain relief.[13] Moreover, Rose *et al.* failed to demonstrate that preoperative DM (0.5 $mg \cdot kg^{-1}$ and 1.0 $mg \cdot kg^{-1}$ *po*) reduced pain and analgesic consumption in children after adenotonsillectomy.[14] Kauppila *et al.* also found that DM (100 mg *po*) did not attenuate the pain produced by topical capsaicin application or ischemia.[15] Pronounced pain relief was observed at a

higher dose, 200 mg, but 50% of the volunteers were withdrawn from the study due to severe side effects.[15] These findings, however, do not necessarily conflict with ours. In Kauppila's study, the effective plasma concentration may not have achieved a sufficient level at the time of assessment by oral intake of a lower dose (100 mg).[15] In McQuay's study, the neuropathic pain syndromes were chronic pain conditions, in which the central nociceptors might have already been sensitized prior to DM administration. Furthermore, the duration of treatment might also have been too short for the chronic pain conditions.[11] In our study, 40 mg DM was prescribed 30 min before surgical incision, when the blood concentration may have reached an effective level. Moreover, the postoperative pain was an acute and short lasting pain condition. Failure to produce analgesia in some reports might have been due to the low oral doses of DM.[11–15] The bioavailability of oral DM is about 10% of the parenteral route. Nelson *et al.* found that a higher oral dose (381 mg·day^{-1}) DM, was comparable with an *im* dose, and provided satisfactory pain relief for painful diabetic peripheral neuropathy.[18]

For the postoperative pain of MRM, the neuropathic pain component predominates over the somatic pain component. In the present study, the analgesic effect of DM on neuropathic and somatic pain may be related to its ability to reduce the spinal cord NMDA receptor activation that may occur following peripheral nerve and tissue injury. Our results support Woolf and Chong's theory that the prevention of the establishment of central nociceptor sensitization may facilitate postoperative pain management.[19] Nelson *et al.* also stated that DM was particularly effective in preventing the consequences of noxious afferent input resulting from ongoing damage to peripheral neuron than in chronic neuropathic pain conditions such as postherpetic neuralgia.[18]

In conclusion, preincisional *im* DM treatment reduced the postoperative pain and meperidine requirement after MRM surgery.

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