Preoperative and Postoperative Dextromethorphan Provides Sustained Reduction in Postoperative Pain and Patient-Controlled Epidural Analgesia Requirement

A Randomized, Placebo-Controlled, Double-Blind Study in Lower-Body Bone Malignancy-Operated Patients

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BACKGROUND. Pain is mediated centrally by N-methyl-D-aspartate (NMDA) receptors. The antinociceptive effects of preincision dextromethorphan (DM), an NMDA antagonist, have been demonstrated in surgical patients under general or epidural anesthesia. The authors investigated the effects of DM on postoperative pain and other parameters in patients undergoing surgery for bone malignancy under standardized combined general and epidural anesthesia using patient-controlled epidural analgesia (PCEA) postoperatively.

METHODS. Patients received placebo or DM 90 mg (30 patients per group) in a double-blind manner preoperatively and on each of the two following days. Postoperative PCEA consisted of 1.6 mg ropivacaine plus 4 µg/mL fentanyl both continuously and by demand up to 96 hours, starting when subjective pain intensity was greater than or equal to 4/10 (visual analog score). Rescue drugs on demand (paracetamol or dipyrene orally) were also available.

RESULTS. The DM patients experienced about 50% (P < 0.01) less pain than their placebo counterparts for more than 2 postoperative days and they rated their overall maximal pain intensity by one-half that estimated by the placebo-treated patients (P < 0.01). The DM group also consumed 30–50% less epidural analgesics than the total amount consumed by the placebo-medicated group (P < 0.05) and demanded significantly (P < 0.05) fewer rescue drugs on the first postoperative day. They were less sedated (40–60%, P < 0.01) and reported 50% fewer overall side effects (P < 0.05). The groups were similar for the need for urinary catheterization, time of first ambulation, and/or discharge home.

CONCLUSIONS. A 3-day DM administration is associated with better pain reduction in patients undergoing surgery for bone malignancy under combined general and epidural anesthesia with postoperative PCEA compared with placebo without increasing side effects. Cancer 2003;97:2334–9. © 2003 American Cancer Society. DOI 10.1002/cncr.11330

KEYWORDS: bone malignancy, surgery, pain, postoperative, patient-controlled analgesia, epidural, dextromethorphan.
lowest effective epidural dose (with patient involvement in determining the amounts needed to control pain).

The role of the N-methyl-D-aspartate (NMDA) receptor in modulating acute pain and the subsequent central sensitization has been well established. The NMDA receptor antagonists reduce pain perception without depressing hemodynamic parameters or respiration, which could have severe consequences. This consideration is most pertinent to patients who undergo surgery for prolonged large musculoskeletal tumor resections and where wakefulness and full orientation are requested postoperatively. Preincision NMDA inhibition preempts the arousal of the spinal cord and inhibits the wind-up process, thus reducing the central perception of pain originating in the periphery. Dextromethorphan (DM) is a noncompetitive NMDA receptor antagonist. Its neurophysiologic activity resembles that of ketamine, but it has a lower rate of side effects, a long history of clinical safety, and it induces preemptive analgesia.

Preoperative oral DM reduces the short-term (6 hours) and long-term (up to 3 days) self-administered morphine and diclofenac requirements following surgery under either epidural or general anesthesia. The beneficial effects of DM have been documented in patients who had undergone surgery under general anesthesia for bone and soft tissue malignancies and who later made use of an intravenous patient-controlled analgesia (IV-PCA) device.

All major (classified below) orthopedic-oncologic procedures in our institution are performed under a combined general and epidural anesthesia technique whenever appropriate. This technique allows better pain control, especially during prolonged orthopedic procedures, and minimizes the amount of general anesthetics. General anesthetics are the main cause of postoperative sedation and disorientation. The current study was designed to assess the benefit of DM to orthopedic oncologic patients who undergo surgery by this combined technique of anesthesia and who are then afforded pain control by PCEA.

MATERIALS AND METHODS
Patient Selection
Sixty patients (American Society of Anesthesiologists [ASA] Physical Status I–III) who underwent lower body bone and soft tissue cancer surgery under combined general and epidural anesthesia were enrolled in this prospective, randomized, double-blind study. The study received approval from the institutional human research and ethics committee. All patients, without exception, experienced preoperative cancer-associated pain that was controlled satisfactorily with non-steroidal antiinflammatory drugs. Each patient gave written consent to participate in the study. Preoperatively, patients were given full explanations from the anesthetist regarding the rationale for DM, the PCA device, and the mode of self-administration of epidural ropivacaine plus fentanyl (PCEA). They were also instructed on how to use the linear visual analog scale (VAS) for pain evaluation.

Surgery consisted of one of the following procedures: 1) resection of a single muscle or a single muscle group with no reconstruction. Bone tumors were treated by local curettage with no segmental resection, as were soft tissue tumors of 8 cm or less diameter with minimal bone involvement. This procedure lasted 3 hours and/or necessitated 3 U or less of blood; 2) large-sized soft tissue resections that necessitated tissue transfer and reconstruction, forequarter amputation, large bone resection and reconstruction, and hemipelvectomy. This procedure involved large bone tumors with or without soft tissue tumors of > 8 cm diameter. This procedure lasted longer than 3 hours and/or necessitated > 3 U of blood.

The same surgical and anesthesia teams performed both procedures. Exclusion criteria were an allergy to fentanyl, bupivacaine, or ropivacaine, the chronic use of any opioids, the use of sedatives or centrally acting drugs (e.g., central nervous system [CNS] depressants or antidepressants) during the 21 days before surgery, or the preoperative use of a central neuroaxial block. Patients younger than age 18 years, pregnant women, and individuals suffering from congenital or acquired neuromuscular disease or chronic pain (unrelated to the current disease) were also excluded. Because significant changes in vital signs (e.g., following epidural placement of the local anesthetic) might affect cognition or pain sensation, a > 20% variation from the values that had been recorded during the premedication visit, or an SpO2 less than 92% under 40% oxygen at any time excluded the patient from the study from that time onwards. Finally, individuals were excluded if their epidural block failed and general anesthesia alone was administered intraoperatively.

Anesthesia and Surgery Protocols
All 60 patients received combined general and epidural anesthesia. Propofol 2–2.5 mg/kg by slow injection was used to induce general anesthesia. Succinylcholine 1.5 mg/kg enabled endotracheal intubation. Fresh gas flows of anesthetics consisted of a 50% mixture of oxygen and nitrous oxide. Propofol was infused intraoperatively at a constant rate of 10–30 μg/kg per minute, atracurium was infused as necessary to facil-
itate artificial respiration and surgical maneuvers, and a fentanyl dose of 0.5–1.0 µg/kg was given to maintain analgesia. The administration of atracurium was stopped approximately 10 minutes before the end of surgery, and nitrous oxide was shut down at the time of placement of the last suture, whereupon the patient inhaled pure oxygen. Neuromuscular relaxation was not reversed pharmacologically as reported in previous studies, and patients resumed spontaneous respiration and were extubated when appropriate.

After general anesthesia was induced, all patients received 0.5% bupivacaine 12–14 mL injected into the epidural space, always at the level of L₄–S₁, aiming to obtain analgesia at the dermatomes T₈–T₁₀. A Portex (SIMS Portex, Hythe, Kent, UK) epidural catheter was inserted and secured in place to enable additional intraoperative administration of the local anesthetic, based on clinical signs.

Intraoperative and postoperative fluids and blood were replaced based on hemodynamic variables, blood loss, hemoglobin levels, and the amount of urine collected via an indwelling urinary catheter. At the end of surgery, the patients were taken to the postanesthesia care unit (PACU) for immediate postoperative assessment.

**Study Groups**

The patients were assigned randomly to two equal groups. One group received 90 mg DM orally and the other received a sucrose-based placebo (in capsules of similar appearance) in a double-blind manner. The DM or placebo was given 90 minutes before surgery. No other premedication was used. The 90-mg dose was selected because lower doses had inconclusive effects on acute pain and postoperative analgesic consumption. In addition, this dose proved to be effective in previous studies. We also wished to avoid the side effects that were self-administered by the patient upon demand, with a lockout time of 15 minutes. The PCEA analgesic protocol also consisted of a background epidural dose of 2 mL per hour of the given drug mixture. The resultant PCEA volume of 8–12 mL per hour was safe and effective to control postoperative pain and has been used in our institution in these patients. Two extra PCEA doses per hour were administered by the attending physician to the patients on demand during their postoperative stay in the PACU.

The following parameters were assessed by the attending physician every 15 minutes for the first hour and every 30 minutes thereafter during each patient’s stay in the PACU. VAS was assessed using the 10-cm chiroscience pain gauge: subjective pain intensity was rated using a VAS from 0 (no pain) to 10 (unbearable pain), and subjective sedation was based on a VAS from 1 (fully awake) to 10 (heavily sedated). Total PCEA consumption was assessed once hourly until the device was disconnected. The rate of PCEA activation was recorded as the number of times the delivery button was pressed. In addition, patients whose daily total use of the device resulted in an activation-to-delivery rate ratio > 1.5 were graded as “relatively excessive” users on that given day.

The time patients left bed for the first time and the day of discharge home were also recorded. When the patients were disconnected from the PCEA, they were asked to score their overall maximal pain intensity throughout the study period. They were also queried on the occurrence of side effects according to a standardized checklist of known adverse reactions attributed to DM, the PCEA, or any of the rescue drugs. This was in addition to the patients’ spontaneous elicitation and the medical staff notes. Side effects were recorded by the protocol-blinded anesthetist in the PACU or by the ward physician and were treated if necessary.

Patients remained in the PACU for 3 hours to monitor possible late-onset pain or sedation. They were then transferred to the Orthopedic Oncology Unit in accordance with the PACU discharge regulations. The PCEA device was continually available to

Postoperative Analgesia and Patient Assessment

Baseline cardiovascular and respiratory parameters were recorded for all patients during the premedication visit. The perioperative and study-long monitoring plan included the measurement of heart rate by a 5-lead electrocardiograph, systolic and diastolic blood pressures, respiratory rate, and fingertip pulse oximetry (AS3™; Datex-Ohmeda, Helsinki, Finland). We chose a cutoff pain intensity score of 4 out of 10 on the VAS based on previous experiences in acute pain control. Upon the patient’s first postoperative complaint of such pain intensity (see below), a PCA device was attached to the patient’s epidural line and activated by the attending anesthetist, who was blinded to the patient’s group assignment and who attended all the patients in the PACU. The study protocol dictated that any patient who exhibited a combative or incoherent state (based on an objective 1–10 scale of coherence where 1 = disoriented, totally incoherent to 10 = fully oriented, and communicating with the staff) while demanding analgesia would be excluded from the study. The physician administered the first bolus of 2 mL (ropivacaine 1.6 mg plus fentanyl 4 µg/mL) epidurally, and this was followed by similar boluses that were self-administered by the patient upon demand, with a lockout time of 15 minutes. The PCEA analgesic protocol also consisted of a background epidural dose of 2 mL per hour of the given drug mixture. The resultant PCEA volume of 8–12 mL per hour was safe and effective to control postoperative pain and has been used in our institution in these patients. Two extra PCEA doses per hour were administered by the attending physician to the patients on demand during their postoperative stay in the PACU.

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each patient for a maximum of 96 hours after surgery. However, if the patient did not use the device for 8 consecutive hours, it was disconnected. During the entire study period, patients were allowed to receive 1 g dipyramone (metamizole, a pyrazolone antiinflammatory agent that inhibits prostaglandin synthesis) or paracetamol orally on demand as a rescue drug.

Statistical Analysis

Statistical analyses were performed using the SPSS Release for Windows, Version 11.01 (SPSS, Chicago, IL). A power analysis had been done in advance to answer the primary question, i.e., What was the effect of DM on PCEA consumption in the patients undergoing surgery? To obtain a power of 0.95 where delta (difference in consumption) = 3 and alpha = 0.05, each study group required an enrollment of 19 patients or more. Demographic data and the various relevant parameters (baseline heart rate, systolic and diastolic blood pressures, respiratory rate, SpO₂, and the mean amounts of fentanyl, propofol, and bupivacaine used intraoperatively) of the two study groups were compared using the one-way analysis of variance (ANOVA). Gender, ASA physical status, and group distribution of surgery type were analyzed using the Pearson chi-square test. The final maximal pain intensity, the day the patients left their beds, and the day they were discharged home were also analyzed by the one-way ANOVA. The square roots of the rates of hourly demands for PCEA administration and the actual use of PCEA were used to obtain their normal distribution. The results were then analyzed by one-way ANOVA with repeated measures. The number of patients in each group for whom the ratio between the hourly demand and actual delivery was greater than 1.5 was compared using the Pearson chi-square test. The number of times the patients received a rescue drug and the rate of side effects were analyzed using the Fisher exact test. The one-way ANOVA tests were always followed by the post hoc Tukey method test. The background data of patients excluded from the study were analyzed following the intent-to-analyze format. All values are expressed as mean ± the standard deviation, with significance defined as $P \leq 0.05$.

RESULTS

Four of the 60 patients originally enrolled in the study were excluded (1 DM patient required prolonged postoperative ventilation, and 3 placebo patients had protocol violations). Table 1 lists the demographic, surgical, and anesthesia data as well as the baseline values of the vital signs, none of which was significantly different between the groups. These values also remained within physiologic ranges throughout anesthesia, surgery, and the study period (data not shown). At no time were there signs of respiratory depression among the patients (i.e., respiratory rate < 6 breaths per minute, SpO₂ < 92% on 40% oxygen). At the end of the 3-hour stay in the PACU, all the patients were discharged uneventfully to the ward, in accordance with the study protocol.

The intensity of pain (by VAS) that was recorded during the PACU phase differed significantly ($P < 0.001$, drug effect) between the groups in favor of the DM group, which also had a better sedation score (Fig. 1, $P < 0.001$). The DM-treated patients reported less pain and sedation than their placebo counterparts as was sedation (Fig. 1). These differences remained almost unchanged for the entire postsurgery period. Pain increased slightly in either group on Days 2 and 3, which may have been attributed to first ambulation. The overall maximal self-rated pain score was also significantly ($P < 0.01$) higher in the placebo group (Table 2).

The total DM group self-administered PCEA during the 3-hour PACU stay was less than one-half that of the placebo group ($P < 0.001$). This difference between the groups in the need for epidural analgesia continued for the first 24 hours following surgery ($P < 0.01$, drug effect; Fig. 2). The mean analgesic requirement started to converge between the groups during the second postoperative day. By the end of the third postoperative day or when the test drugs were

![Table 1](image_url)

**Table 1.** Demographic Information, Anesthesia, and Surgery Data, and Baseline Vital Signs

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>Placebob</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>50 ± 21</td>
<td>42 ± 19</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 ± 18</td>
<td>70 ± 15</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>16/14</td>
<td>17/13</td>
</tr>
<tr>
<td>ASA (no. of patients, Class 1/2)</td>
<td>8/22</td>
<td>6/24</td>
</tr>
<tr>
<td>Surgery (no. of patients, Class 1/2)</td>
<td>11/19</td>
<td>12/18</td>
</tr>
<tr>
<td>Intraoperative fentanyl (mg)</td>
<td>71 ± 9</td>
<td>68 ± 6</td>
</tr>
<tr>
<td>Intraoperative bupivacaine (mL)</td>
<td>18 ± 5</td>
<td>21 ± 7</td>
</tr>
<tr>
<td>Intraoperative fluid administration (mL)</td>
<td>3540 ± 685</td>
<td>3850 ± 595</td>
</tr>
<tr>
<td>Intraoperative blood replacement (U)</td>
<td>4.2 ± 1.1</td>
<td>3.8 ± 1.0</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>127 ± 47</td>
<td>150 ± 104</td>
</tr>
<tr>
<td>Baseline vital signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76 ± 14</td>
<td>82 ± 15</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>13 ± 6</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>120 ± 13</td>
<td>118 ± 16</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>66 ± 8</td>
<td>69 ± 8</td>
</tr>
<tr>
<td>Pulse-derived oximetry (SpO₂, %)</td>
<td>98 ± 1</td>
<td>98 ± 3</td>
</tr>
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ASA: American Society of Anesthesiologists physical class.

bIncludes data of the four excluded patients (intent-to-treat analyses). There were no significant statistical differences between the groups.

*Mean ± standard deviation.*
stopped by protocol, PCEA was still in use in 12 placebo patients, compared with 6 DM patients \( (P = 0.02 \) by the Fisher exact test). The number of patients who used the PCEA device excessively was significantly \( (P < 0.05) \) higher in the placebo group compared with the DM group (Table 2). The rate of overall demand for the rescue drugs in addition to the PCEA was higher \( (P < 0.05) \) in the placebo group throughout the study period, particularly on Day 1 postoperatively (Table 2).

More \( (P < 0.05) \) placebo patients than DM patients suffered side effects, consisting almost exclusively of nausea, pruritus, and vomiting. These were promptly and satisfactorily alleviated by appropriate medications (Table 2). Nevertheless, the number of patients who required bladder catheterization for more than 24 hours after surgery, the day the patients left their beds for the first time, and the day they were discharged home were similar between both groups (Table 2). It is noteworthy that there were no cases of motor blockade of the lower limbs that prevented early ambulation.

**DISCUSSION**

The beneficial effects of preincision and postincision oral DM on postoperative pain control, in terms of attenuating morphine and oral analgesics consumption, were first studied in patients undergoing general surgery.\(^2,8,16\) The effectiveness of DM in surgical patients who had epidural analgesia was assessed in earlier reports.\(^8,9\) In addition, another study cohort similar to the current one showed that IV-PCA morphine and other subjectively rated parameters were better in patients who received DM.\(^10\) We investigated the possible benefits of DM in patients undergoing major surgery for lower-body bone malignancy under combined general and epidural anesthesia with postoperative PCEA-administered analgesia.

The combined general and regional anesthesia technique preempted perioperative pain\(^19\) and tem-
temporarily reduced the levels of stress hormones, anxiety, and depression compared with general anesthesia alone.\textsuperscript{12,13} We reasoned that it would be especially suitable for patients undergoing extensive and painful procedures compared with general surgery patients and patients undergoing limited oncologic procedures.\textsuperscript{10} Early ambulation is a prerequisite for preventing postoperative thromboembolization. This was another consideration for using postoperative PCEA rather than IV-PCA–delivered analgesia associated with perioperative DM.

Our immediate (3 hours) and late (up to 4 days) postoperative results demonstrated the antinociceptive effects of DM. Both the epidural rate of consumption and the oral rescue drug requirements in the DM-treated patients were lower by approximately one-half of that for the matched patients who received the placebo. This difference, which was almost constant throughout the 3-day study, indicates the antinociceptive additive effect of DM over PCEA. There were also fewer DM patients who used PCEA excessively. By the end of the 3-day test-drug treatment period, PCEA was still being used by 40% of the placebo-administered patients compared with only 20% of the DM patients. In addition, lowering of subjective pain intensity in the DM group was achieved without increasing sedation. The rate of side effects was lower in the DM group, but DM and placebo patients had a similar time to ambulation and time to discharge.

The use of PCEA after the combined anesthesia technique was beneficial to patients who were already experiencing pain preoperatively. The positive effect of DM on postsurgery pain intensity and on analgesic consumption is better than that reported in an earlier study on IV-PCA–administered DM.\textsuperscript{10} This may be due to a drug interaction that preempts pain.\textsuperscript{7,20} The association between the epidural techniques and DM is clinically important. Unlike other clinical DM studies,\textsuperscript{2,5,8,16,21} the patients in the current study suffered from a variable degree of preoperative pain. We contend that the surgical procedure of our current study patients “reignited” a “silent” status of hyperexcitability and wind-up conditions within the CNS that had been established during these preoperative episodes of pain. This sequence of events, i.e., a silent hyperexcitable state and subsequent activation, is supported by a recently described phenomenon in the brain of rats where the rostroventral medulla region of the brain signaled the dorsal horn of the lumbar spinal cord.\textsuperscript{22} Once silent synapses have been activated, as during surgery, they remain functionally active and continue to send messages to the brain even when there is an otherwise acceptable level of a painful stimulus. For example, the intense pain generated in-}

itraoperatively and postoperatively could have transformed the latent hyperexcitability into an active status. Because the latent hyperexcitability could respond to frequent peripheral sensory nerve stimulation that had not heretofore evoked overt hyperactivity within the spinal cord, we opted for the use of perioperative epidural analgesia. Glutamate is one of the excitatory amino acids involved in the activation of NMDA receptors during the process of hyperexcitability, which further explains our successful use of DM in attenuating pain in this particular group of patients.

Previous studies have reported additive effects between other NMDA antagonists and local anesthetics. For example, ketamine plus epidural morphine and lidocaine anesthesia provided better postoperative analgesia than ketamine and systemic morphine combined with general anesthesia.\textsuperscript{23} Our current data are also supported by the recent findings that both NMDA and the non-NMDA glutamate receptor antagonists interact with lidocaine synergistically at the spinal level.\textsuperscript{24} Therefore, the preemptive techniques of the epidural analgesia and DM administration were probably responsible for the perceived low pain intensity levels.

No patients withdrew from the current study, and all side effects were temporary and tolerable. From an overall clinical prospective, despite the possible effects of epidural ropivacaine, this and DM did not depress the cardiovascular parameters and there were no detectable signs of respiratory or neurologic depression despite the addition of fentanyl to the epidural solution. The overall reduced number of side effects compared with a previous study in which IV-PCA was administered to patients with even less severe orthopedic and oncologic conditions supports our contention that morphine and general anesthesia had been the main cause\textsuperscript{10} The DM protocol is thus a promising and safe medication for patients with severe orthopedic and oncologic disease. Lower body bone disease is associated with the use of high doses of analgesics because of a lower threshold of pain, especially for individuals with a history of radiotherapy or chemotherapy and other debilitating procedures that are known to induce pain, nausea, and vomiting.\textsuperscript{1,25}

There was a lack of statistical difference between groups with regard to first ambulation and discharge home. The patients in the current study were discharged later than the patients in the earlier Weinbroum et al. study,\textsuperscript{10} probably because of the larger portion of “Type 2” procedures performed. Future studies focusing on this issue may be necessary due to the importance of early ambulation and its association with a low rate of postoperative complications.\textsuperscript{26}

In conclusion, oral DM at a dosage of 90 mg once
preoperatively and for 2 days postoperatively reduced pain intensity, minimized sedation, and spared PCEA and oral rescue drugs up to 4 days after lower-body bone malignancy surgery under combined general and epidural anesthesia. The administration of DM at the described dose did not augment the rate of side effects, but neither did it affect the time to ambulation and discharge home. The results of this evaluation of DM in patients with severe postoperative pain suggest that the pain control techniques we applied in this study constitute a safe and promising approach that warrants further clinical confirmation.

REFERENCES


