Duloxetine reduces morphine requirements after knee replacement surgery

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Multimodal analgesia utilizes a combination of opioids and non-opioids to target various sites in the central and peripheral nervous system to manage postoperative pain. The objective is to minimize opioid use and, therefore, opioid-related adverse effects or opioid-induced hyperalgesia. Tissue trauma resulting from surgery can also sensitize peripheral nociceptors leading to central neuronal sensitization. Therefore, the use of adjuvants such as ketamine, gabapentinoids (gabapentin and pregabalin), and clonidine has been shown to be useful in perioperative pain management. Appropriate management of postoperative pain is also important as the intensity of acute postoperative pain has been shown to increase the risk of chronic post-surgical pain.

Serotonin and norepinephrine may modulate descending inhibitory pain pathways in the central nervous system (CNS). Duloxetine, a potent selective serotonin and norepinephrine reuptake inhibitor (SNRI), has been shown to be effective in treating chronic pain. A recent animal study also demonstrated that the norepinephrine reuptake inhibitor maprotiline increased morphine anti-nociceptive activity when administered intrathecally. Therefore, duloxetine may have a role in reducing postoperative pain, especially when combined with opioid therapy.

The primary aim of our study was to investigate the efficacy of duloxetine in reducing morphine requirements after knee replacement surgery. Secondary aims include reduction in postoperative pain scores, adverse effects, and the incidence of chronic postoperative pain at 3 and 6 months after surgery.

Methods

The study was approved by our hospital Institutional Review Board (Ref: 127/2008). Written informed consent was obtained from all subjects. The primary objective was to...
evaluate the efficacy of two doses of oral duloxetine 60 mg in reducing morphine requirements in patients undergoing elective knee replacement surgery at Singapore General Hospital. The design and conduct of our trial adhered to the CONSORT Statement.9 10

Patients between the ages of 18 and 70 yr and of ASA physical status I–III were eligible for the study. Patients were recruited from the Department of Orthopaedic Surgery between August 2008 and May 2009. The inclusion criteria were: a known allergy to duloxetine or morphine, pre-existing pain syndrome and/or analgesic treatment (excluding acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and Cox-2 inhibitors), a history of drug or alcohol abuse, and abnormal renal and liver function tests. Oral analgesics were discontinued 24 h before surgery.

Standard monitoring include electrocardiography, non-invasive arterial pressure measurement, pulse oximetry, and capnography. Patients were routinely offered a single-shot spinal anaesthesia consisting of an intrathecal dose of bupivacaine 10–12.5 mg with fentanyl 10 μg. Patients who refused or have contraindications to a regional anaesthetic were given general anaesthesia (GA). Anaesthesia was induced with i.v. propofol 2 mg kg⁻¹ and fentanyl 1–2 μg kg⁻¹. A laryngeal mask airway was then inserted. Anaesthesia was maintained with sevoflurane 2.0–3.0% in an air–oxygen mixture containing 40% oxygen. Patients were allowed to breathe spontaneously. During surgery, titrated doses of morphine up to a total of 0.1 mg kg⁻¹ was administered by the anaesthetist in accordance with standard practice to maintain the patient’s heart rate and arterial pressure within 20% of preoperative baseline. The same three orthopaedic surgeons performed the knee replacement surgery using the same approach.

After surgery, pain treatment consisted of patient-controlled analgesia (PCA) with i.v. morphine. The settings were 1 mg bolus, 5 min lockout time, and a maximum hourly limit of 8 mg. All patients were also given acetaminophen 1 g 6 hourly. NSAIDs were prohibited for the purpose of this study.

The study was a parallel group, double-blind, randomized, placebo-controlled trial. Patients received either oral duloxetine 60 mg or identical matching placebo capsules 2 h before surgery and on the morning of the first postoperative day. Study medication was marked with consecutive numbers according to a computer-generated table of random numbers. Patients were assigned consecutively to their group according to their number. Randomization and allocation were only revealed for data analysis when the study was completed and the required number of subjects had been recruited. The patients did not receive any premedication.

A blinded observer who was not part of the anaesthesia team or study team followed up with the patients. The primary outcome measure was total morphine requirements at 48 h after surgery. The secondary outcome measures were pain scores at rest and on movement (i.e. mobilization during physiotherapy) and the presence or absence of adverse effects such as headache, nausea, vomiting, dizziness, and somnolence. Pain scores were recorded at 0.5, 1, 2, 6, 12, 24, and 48 h after surgery on an 11-point numeric rating scale (NRS) (with ‘0’ being ‘no pain’ and ‘10’ being the ‘worst possible pain’).

Before discharge from the hospital, all patients were prescribed with acetaminophen 1 g 6 hourly, etoricoxib 120 mg daily and tramadol 50 mg 8 hourly for 2 weeks. They were instructed to note the amount of pain they had at home and their analgesic needs. We defined chronic pain as the presence of pain 3 months after surgery, independent of its intensity or analgesic requirements. Three and 6 months after surgery, patients were interviewed via telephone, by an anaesthetist blinded to their treatment group, regarding any pain, abnormal sensation (allodynia, hyperalgesia, dysaesthesia, or hypoalgesia), or both at the surgical site. The presence of pain (‘yes’ vs ‘no’ pain), the pain intensity (NRS; 0–10), and the analgesic requirements at home, if any, were recorded.

Initial sample size estimation was based upon morphine consumption in a retrospective sample of 50 patients who received knee replacement surgery in our department. Approximately 24 patients in each group were required for a power of 0.80 at an α level of 0.05 for detecting a 50% difference in morphine consumption between groups at 48 h post-surgery.

SPSS 17 software was used for statistical analysis (SPSS Inc., Chicago, IL, USA). A value of P < 0.05 was considered significant. Patient characteristics, duration of surgery, and anaesthesia were compared between groups with two-tailed unpaired t-test. To assess for normality on the data set, the Shapiro–Wilk test was performed. Data were presented as median (with inter-quartile range) or mean [with standard deviation (SD)] as appropriate. Assumption of normality was rejected for most data, and consequently, the non-parametric Mann–Whitney U-test for independent samples was used for comparison. Significant Mann–Whitney U values were Bonferroni corrected for the various time points investigated. Rates of adverse effects and the number of patients in each group who required analgesics for chronic pain 3 and 6 months after surgery were compared using χ² test or Fisher’s exact test.

Results
From August 5, 2008 to May 22, 2009, 58 consecutive patients who fulfilled inclusion criteria were eligible for the study (Fig. 1). Seven patients refused to participate and one patient had newly diagnosed impaired renal function. Therefore, 50 patients were randomized and included in the study. However, three patients were subsequently excluded, resulting in data from 47 patients in the final analyses. Patient and clinical characteristics for each group (Table 1) showed no significant differences between the groups.

The morphine requirement at 24 h was 12.9 mg (SD 10.4 mg) in the duloxetine group and 19.8 mg (SD 13.7 mg) in the placebo group (P = 0.039). At 48 h, total morphine...
Requirement was significantly lower in the duloxetine group (19.5 mg, SD 14.5 mg) compared with the placebo group (30.3 mg, SD 18.1 mg) ($P=0.017$) (Fig. 2). When patients who received regional anaesthesia (RA) were analysed separately, morphine requirement was still significantly lower in the duloxetine group at 48 h post-surgery ($P=0.033$).

There were no statistically significant differences in pain scores at rest and on movement at all time points between the placebo and duloxetine groups (Table 2). When patients who received RA were analysed separately, the difference in pain scores at rest and on movement was not statistically different between placebo and duloxetine groups ($P>0.05$).

The most common adverse effect experienced by subjects in the study was nausea and vomiting (Table 3). All affected patients responded to i.v. ondansetron. No statistically significant differences were noted between groups.

At the third and sixth month after surgery, two patients in the placebo group and one in the duloxetine group could not be contacted. In addition, one patient in the duloxetine group died from pneumonia 6 months after surgery. Twenty-two patients in the placebo group and 21 patients in the duloxetine group were contacted (Table 4). At the 3 month follow-up, the presence of abnormal sensation at the surgical site was reported in 10 patients in the placebo group and four patients in the duloxetine group ($P=0.065$). Six patients in the placebo group reported residual pain at 3 months post-surgery (mean NRS-pain intensity 3/10). Pain resolved in only one of these patients in the placebo group after 6 months. In comparison, residual pain was reported in two patients at 3 and 6 months in the duloxetine group (mean NRS-pain intensity 2/10) ($P=0.41$). No statistically significant difference was noted.

## Discussion

Perioperative oral administration of two doses of duloxetine 60 mg resulted in reduction in morphine requirements at 24 and 48 h after surgery. However, pain scores at rest and
on movement were not significantly different statistically between groups at all time points. No significant difference in adverse effects or residual pain after 3 months from the surgery was observed between duloxetine and placebo in this study.

Surgical tissue injury results in both peripheral and central sensitization. Such neuroplastic changes can manifest as hyperalgesia or allodynia in patients after surgery.11 As such, ‘antihyperalgesic’ drugs have been used as adjuvants as an integral part of multimodal analgesia.3 Gabapentin and pregabalin bind the α-2-δ-subunit of voltage-dependent calcium ion channels to block the development of hyperalgesia and central sensitization. Both drugs have well-established roles in the treatment of neuropathic pain. The perioperative administration of gabapentin or pregabalin has been shown in clinical trials and meta-analyses to be effective in reducing pain scores, opioid requirements, and opioid-related adverse effects after surgery.12–16

Duloxetine is a selective SNRI that is efficacious in chronic pain conditions such as painful diabetic neuropathy and fibromyalgia.6,7 A recent Cochrane review also supports the efficacy of duloxetine 60 and 120 mg in treating pain in diabetic peripheral neuropathy and fibromyalgia.18 As there were no previous trials evaluating the role of duloxetine in acute pain, we chose duloxetine 60 mg dose in this study based on doses used for chronic neuropathic pain. Doses 60 mg were not found to be efficacious.18 The possible mechanism of action of duloxetine in our study could be explained by the central pain inhibitory action secondary to the potentiation of serotonergic and noradrenergic activities in the CNS. Mean NRS-pain scores in both groups were throughout the entire study period. Patients had access to i.v. PCA morphine and were instructed to use it to administer morphine as and when they experienced pain. Therefore, we believe that morphine requirement is an appropriate surrogate indicator of the intensity of postoperative pain in our study.

The anaesthetic technique during surgery may have a clinical impact on immediate postoperative pain scores, in that patients who received GA might have more pain in the first few hours after surgery than patients who received RA. However, a subgroup analysis of patients who received RA...
showed similar effects on morphine requirements to those in the whole group. It was also noted that pain scores appeared to be slightly higher in the first few hours after surgery in the duloxetine group compared with the placebo group. However, this was not statistically significant and also unlikely to be clinically important as pain scores remained <3 in both groups. Nevertheless, this might be related to the fact that peak plasma concentration of duloxetine is only achieved about 6 h after oral administration.

Our study showed that the incidence of adverse effects such as sedation and dizziness were similar between the duloxetine and placebo groups. Previous studies of gabapentin or pregabalin with placebo have demonstrated an increased incidence of sedation or dizziness with such adjuvants. Our finding may suggest that duloxetine can be an useful alternative to the gabapentinoids as it does not increase drug-related adverse effects. However, our study was not powered to detect any real difference in adverse effects between the two groups.

Although there appeared to be a smaller number of patients who reported abnormal sensation or pain in their operated knees after taking duloxetine, this was not statistically significant and our study was not powered to detect this. Larger sample sizes would be needed to evaluate this finding further.

There are several limitations to our study. First, patients undergoing both GA and RA were allowed to participate in this trial. We did not confine the inclusion criteria to patients receiving only one type of anaesthetic because we chose to adopt a pragmatic study design to reflect routine practice. Patients undergoing knee replacement surgery in our institution were routinely offered a choice of GA or RA (subarachnoid block). Secondly, the detection of chronic pain or abnormal sensitization 3 and 6 months after surgery was carried out via a phone interview. Patients did not return to the hospital to be examined objectively and this might give an inaccurate representation of the true nature of pain or abnormal sensitization over the operated knee.

In conclusion, our study showed that perioperative administration of two doses of duloxetine 60 mg was efficacious in reducing morphine requirements in the 48 h after knee replacement surgery. Duloxetine can be a useful adjuvant when used with opioids, non-opioids, and regional analgesic techniques as part of a multimodal approach in postoperative pain management. Data from our study are only preliminary in nature. Further work should explore larger patient samples and a longer duration of duloxetine administration. The use of duloxetine in surgery associated with greater postoperative pain or surgery that has a higher risk of chronic pain development (e.g. thoracotomy, amputation, mastectomy and inguinal herniorrhapy, etc.) should also be investigated.

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Conflict of interest

None declared.

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Table 4 Three and 6 month follow-up for residual surgical site pain

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<thead>
<tr>
<th>Follow-up</th>
<th>Placebo (n = 22)</th>
<th>Duloxetine (n = 21)</th>
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