Hip fractures are common fragility fractures and their incidence has increased as the proportion of the elderly population increases. There are approximately 70,000 cases annually in the United Kingdom and this figure will double by 2050. There is now a national effort to standardize the management of patients with hip fractures, including guidelines issued by the British Orthopaedic Association and the National Institute of Clinical Excellence (NICE). In these published guidelines, providing for adequate analgesia for hip fracture patients is a major priority on admission to the hospital and prior to surgery. In the United Kingdom, the admitting orthopedic team has responsibility for this pain management.

The customary practice is to follow the World Health Organization analgesic ladder, originally designed 20 years ago for cancer pain management. The principles of these recommendations are: nonopioid medication for mild pain; mild opioids and adjuvant medication for moderate pain; and strong opioids and other adjuvant medication for severe pain. The NICE guideline, published in June 2011, included analgesia recommendations for hip fracture patients in the United Kingdom. After assessing the pain level of the patient, regular doses of paracetamol should be the first agent for pain control. Opioid medications are added according to requirements of the individual patient. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is not recommended because of their association with peptic ulcers and renal impairment. A local nerve block, such as a femoral block, may be useful in reducing analgesic medication preoperatively, but this should only be provided by trained personnel. Surgical treatment of the hip

Can Intravenous Paracetamol Reduce Opioid Use in Preoperative Hip Fracture Patients?

KAI S. TSANG, MRCS(ENG); JON PAGE, FRCS(ORTHO); PAUL MACKENNEY, MD, FRCS(ORTHO)

abstract

Pain due to intra- and extracapsular hip fractures is usually treated with opioid medication. Paracetamol (acetaminophen in North America) has better bioavailability when given intravenously than orally and has been successfully used in the postoperative care of orthopedic patients. However, no study has evaluated its use in the preoperative trauma patient. Our unit conducted a prospective, consecutive cohort study to investigate the opioid-sparing effect of regularly administered intravenous paracetamol compared with oral paracetamol in preoperative hip fracture patients. The total opioid dose given, based on conversion to intravenous morphine, and the reported pain score were evaluated in 75 patients. There were 28 patients in the control group who were given routine oral paracetamol and oral opioids, with morphine for breakthrough pain. There were 47 patients in the study group who received only routine intravenous paracetamol, with opioids reserved for breakthrough pain. The patients in the 2 groups had similar characteristics. The mean preoperative oral paracetamol dose for the control group was 7.2 g compared with 6.3 g in the study group. There was a significant reduction (P<.005) in the mean total intravenous morphine with intravenous paracetamol (6.5 mg) compared with oral paracetamol (21.8 mg). There was no difference in the mean pain score between the groups, 2.1 vs 1.8 (P=.3). Intravenous paracetamol had a significant opioid-sparing effect and satisfactory pain relief in preoperative hip fracture patients.

The authors are from the Trauma and Orthopaedic Department, James Cook University Hospital, Middlesbrough, United Kingdom. Drs Page and Mackenney received payment to their institution from Bristol-Myers Squibb for lecture and travel expenses. Drs Tsang, Page, and Mackenney were compensated by SLACK Incorporated for their contributions to this manuscript. Correspondence should be addressed to: Kai S. Tsang, MRCS(Eng), Trauma and Orthopaedic Department, James Cook University Hospital, Marton Rd, Middlesbrough, UK (kst596@doctors.org.uk).

doi: 10.3928/01477447-20130122-53
Fracture is the definitive analgesia, but this may be delayed due to medical comorbidities or logistic reasons.

The optimal analgesic regimen in this elderly population is controversial. Opioid medication, particularly intravenous morphine, is a strong analgesic, but these may have serious adverse effects in the elderly patient. These adverse reactions include nausea, vomiting, constipation, confusion, respiratory arrest, and even death.7 The pharmacokinetics of opioid medication in the elderly population is poorly understood.8 Opioid metabolism and excretion are determined by both hepatic and renal function, both of which may be suboptimal in the elderly population. We have had elderly patients experience respiratory arrest after a single dose of morphine.

Oral paracetamol is a safe analgesic, but its bioavailability when given orally can be reduced by the first-pass hepatic metabolism up to 40% and its gastrointestinal absorption could be slowed by concomitant opioid administration.9 Intravenous paracetamol has been available in the United Kingdom since 2004, but, to our knowledge, has not been studied for preoperative management in trauma patients. An earlier prototype of intravenous paracetamol has proven to be an effective, safe, and opioid-sparing analgesic agent in orthopedic postoperative care10,11 and in other disciplines.12,13 A recent review in the National Electronic Library for Medicine14 has reaffirmed the superior efficacy of intravenous paracetamol as an analgesic agent. In an effort to improve safety while maintaining good analgesia, our orthopedic team was advised to consider a preoperative intravenous paracetamol-based analgesic regime for patients with hip fractures.

**Materials and Methods**

We performed a prospective, consecutive cohort study in 2008 at one hospital in the United Kingdom. According to the guidelines of the National Research Ethics Service,15 this study was considered a clinical audit and did not require a Research Ethics Committee approval. As an audit proposal, this study was submitted to and approved by the local hospital authority. Data were collected prospectively on adult patients (>15 years) with an intracapsular or extracapsular hip fracture admitted under the care of the senior author. Polytrauma patients, patients on chronic opioids before injury, and those patients considered medically unfit for surgery were excluded.

The first part of the study was to determine the opioid use in hip fracture patients based on the World Health Organization pain ladder guidelines. These patients received regular oral paracetamol (1000 mg 4 times every 6 hours) together with regular oral opioid medication. Our unit used either codeine phosphate or tramadol as regular oral opioid analgesics and intravenous morphine was reserved for breakthrough pain. To standardize opioid measurement, oral opioid doses were converted into an intravenous morphine equivalent dose. The conversion rate for oral opioids into intravenous morphine was adopted from the UK Department of Health,16 with 1 mg of intravenous morphine considered equivalent to 2 mg of oramorph (oral morphine), 20 mg of codeine, or 10 mg of tramadol. The pain level of these patients was routinely recorded by the nursing staff on the trauma ward, using a visual analogue pain scale of 0 to 10, with 10 signifying maximal pain. The adverse effects of opioids are difficult to quantify but are usually dose dependent. For this study, we decided to measure the total opioid dosage used preoperatively, from time of admission to the anesthetic room and the average preoperative pain score of these patients. Patient age, gender, ASA grade, mini-mental state examination, and time to surgery for these patients were routinely recorded.

In the second cohort of this study, a new analgesic regimen was introduced to hip fracture patients under the care of the senior author, with the use of intravenous paracetamol (1000 mg every 6 hours) preoperatively on a regular basis. Oral and intravenous opioids were used only to control breakthrough pain. The same demographic data, total opioid dose used, and mean preoperative pain score were recorded. Patients in the first cohort served as the control group and those in the second cohort were termed the intervention group.

Statistical analysis was performed using a 2-sample t test, assuming equal variances, to calculate any statistical significance in the observed differences between the 2 groups.

**Results**

In the first cohort or control group, there were 28 patients, 26 women and 2 men, with a mean age of 81 years (range, 50 to 97 years), and a mean mini-mental score of 6.7 (scale of 1 to 10). There were 13 extracapsular and 15 intracapsular fractures. The mode American Society of Anesthesiologists (ASA) grade was 3 (range, 2 to 5). The mean time to surgery was 2.6 days, with a mode of 1 day, and a range of 1 to 8 days. The mean total oral paracetamol dose given preoperatively was 7.2 g. The mean total intravenous morphine dose given preoperatively (including converted opioid doses) was 21.8 mg. The mean pain score preoperatively was 2.1 (scale of 1 to 10).

In the second cohort or intervention group, there were 47 patients, 33 women and 14 men, with a mean age of 79.5 years (range, 57 to 100 years), and a mean mini-mental score of 6.6 (scale of 1 to 10). There were 19 extracapsular and 28 intracapsular fractures. The mode ASA grade was 3 (range, 1 to 4). The mean time to surgery was 2.2 days, with a mode of 1 day, and a range of 0 to 6 days. A comparison of the demographics of the 2 cohorts showed no statistically significant differences (Table 1). The mean total intravenous paracetamol dose given preoperatively was 6.3 g.
The mean total intravenous morphine dose was 6.5 mg (Figure 1). The mean preoperative pain score was 1.8 (Figure 2).

There was no significant difference between the mean age of the 2 groups ($P=14$) and the time to surgery ($P=.17$) (Table 2). There was no significant difference between the dose of paracetamol used by the 2 groups ($P=.23$), although the method of administration was different. The reduction in mean morphine dose was 70% and this was statistically significant ($P<.005$). Opioid dose decreased as patient age increased (Table 3). There was no significant difference in the mean pain score between the 2 groups ($P=.30$).

To evaluate if the higher morphine dose preoperatively in the first cohort or control group was due to a longer waiting time to surgery, a recalculated morphine dose per day was performed. The mean morphine dose per day in the first cohort or control group was 9.0 mg per day and 3.8 mg per day in the second cohort or intervention group, a reduction of 58% and statistically significant ($P<.005$).

There were no complications in either group in the preoperative period.

**DISCUSSION**

Paracetamol is a well known analgesic and antipyretic agent that was underutilized for many decades due to concerns about a hematological side effect. However, a reevaluation led to the reentry of oral paracetamol into the United Kingdom market in 1956. Considering the advantage of paracetamol compared with NSAIDs and opioid medication with respect to adverse reactions, a parenteral form was developed for cases when oral medication could not be taken. The first widely used intravenous paracetamol in the United Kingdom was Perpalgan (Bristol-Myers Squibb, Uxhall, Middlesex, United Kingdom), which used hydrophilic ingredients, like mannitol and disodium phosphate, to make it soluble and a pH buffer of sodium hydroxide and disodium phosphate to control hydrolysis.

The obvious advantage of intravenous compared with oral paracetamol is the avoidance of first-pass hepatic metabolism. In addition, the gastrointestinal absorption of paracetamol is less reliable perioperatively in fasting and stressed patients. The analgesic effect of paracetamol begins within 5 minutes of infusion, reaching its peak at 1 hour with a half life of 4 to 6 hours, according to the product information. One study showed that intravenous paracetamol was superior to the oral form in achieving the therapeutic level and in maintaining a higher plasma concentration in patients. The major clearance of paracetamol metabolites is via renal excretion.

The plasma concentration of intravenous paracetamol was reported to be approximately 50% greater in patients older than 80 years compared with patients between 20 and 40 years. The repeated use of intravenous paracetamol has also proven to be safe provided it is kept within the daily dose limit of 4000 mg. The intravenous paracetamol dose should be adjusted for patients weighing less than 50 kg.

The major weakness of this study is that it is not a prospective randomized study. We considered this design, but decided it was technically and ethically not...
hypothetical content


