The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: a randomised, double-blind, controlled study

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Summary
Ketamine and pregabalin each provide postoperative analgesia, although the combination has yet to be evaluated. One hundred and forty-two patients undergoing total hip arthroplasty were randomly assigned to receive ketamine alone, pregabalin alone, ketamine and pregabalin combined, or placebo. Pain scores at rest and on movement, morphine consumption, side-effects, pressure pain thresholds and secondary hyperalgesia were evaluated. Mean (SD) total 48-h morphine use was reduced in patients given ketamine alone (52 (22) mg) and pregabalin alone (44 (20) mg) compared with placebo (77 (36) mg) p < 0.001. Morphine use was further reduced in patients given both ketamine and pregabalin (38 (19) mg) with an interaction between ketamine and pregabalin (ANOVA factorial; p = 0.028). Secondary hyperalgesia was reduced by ketamine. There were no differences between groups in pain scores after surgery, pressure pain thresholds or side-effects. The combination of pregabalin and ketamine has a small, beneficial clinical effect.

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Introduction
Patients experience moderate to severe pain after total hip arthroplasty. Patient-controlled opioid analgesia is usually effective for treatment of pain at rest, but often provides inadequate analgesia for movement and may provoke side-effects that can delay hospital discharge. In addition, recent data suggest that postoperative hyperalgesia may intensify postoperative pain [1, 2]. Thus, drugs that both reduce postoperative hyperalgesia and limit acute postoperative pain may be of clinical interest.

Peri-operative intravenous administration of low-dose ketamine helps to control acute and persistent pain [2–5]. Ketamine is a non-competitive N-methyl-D-aspartate receptor antagonist offering preventive analgesia [3]. Ketamine also reduces secondary hyperalgesia after surgery, even when given as a single intra-operative bolus of 0.5 mg.kg⁻¹ [1, 2, 4, 6, 7]. Postoperative ketamine also reduces opioid consumption but is frequently associated with neurological side-effects [8].

Gabapentinoids bind pre-synaptically to the δ subunit of the calcium channel, which reduces release
of inflammatory neurotransmitters including glutamate, substance P and calcitonin gene-related peptide [9]. Animal studies demonstrate that pregabalin reduces hyperalgesia related to inflammation or opioid [10, 11]. Pregabalin use has been investigated over a variety of regimens including a single pre-operative bolus and repeated administration for two postoperative weeks [12, 13]. Pregabalin seems to have some impact on acute pain after surgery [12].

It seems likely that both ketamine and gabapentinoids can attenuate neuronal hyperexcitability through different and potentially additive mechanisms. Consistent with this theory, a recent study of opioid-induced hyperalgesia in rats identified a synergistic interaction between gabapentin and ketamine [14].

Total hip arthroplasty causes moderate to severe postoperative pain. Both ketamine [2] and pregabalin [15] reduce acute pain after total hip arthroplasty. Whether the combination of ketamine and pregabalin can further improve analgesia after surgery remains unknown. Consequently, this study evaluated the analgesic effects of ketamine and pregabalin alone and in combination after total hip arthroplasty. Our primary outcome measure was morphine consumption after surgery. Our secondary outcome measures were intensity of acute postoperative pain, incidence of opioid-related side-effects and secondary hyperalgesia after total hip arthroplasty.

Methods

With the approval of the Local Research Ethics Committee (Comité de Protection des Personnes pour la Recherche Biomédicale, hôpital Ambroise Paré Boulogne 92) and patients’ written informed consent, a prospective, two centre, randomised double-blinded study was undertaken (Eudra CT number 2009-010859-27). Patients recruited were of ASA physical status 1–3, between 18 and 80 years and scheduled for total hip arthroplasty under general anaesthesia. Exclusion criteria were a posterior surgical approach, regional anaesthesia, contraindications for ketamine, pregabalin or morphine use, severe cardiac, renal or hepatic diseases, and pre-operative use of corticosteroids and/or opioids.

Computer-generated randomisation (Excel; Microsoft Office 2007) was based on blocks of four patients. Allocations were concealed in sequentially numbered sealed opaque envelopes, which were opened the day before surgery after patients had consented to the trial. Pregabalin was prepared by the Pharmacy Department by over-encapsulating a 150-mg pregabalin capsule. The identically-appearing placebo consisted of the same large capsule filled with lactose. Two syringes were prepared in the operating room by a nurse not involved in the evaluation of the patients. For ketamine, a 5-ml syringe was prepared for an initial bolus of 0.5 ml.kg\(^{-1}\); a 20-ml syringe was prepared for a continuous 0.18 ml.kg\(^{-1}.h^{-1}\) intra-operative infusion. According to the randomisation assignment, these syringes were filled with ketamine solution (1 mg.ml\(^{-1}\)) or saline 0.9%. None of the other investigators involved in patient management or data collection was aware of the group assignment.

Patients were randomly assigned to receive one of the following four treatments: (i) placebo ketamine and placebo pregabalin (placebo); (ii) intravenous ketamine with a 0.5 mg.kg\(^{-1}\) bolus at the time of anaesthesia induction immediately followed by a 3 µg.kg\(^{-1}.h^{-1}\) infusion stopped at skin closure and placebo pregabalin (ketamine alone); (iii) oral pre-operative pregabalin 150 mg and placebo ketamine (pregabalin alone); (iv) the combination of these same doses of ketamine and pregabalin (ketamine and pregabalin).

Patients were premedicated with 1–2 mg.kg\(^{-1}\) hydroxyzine orally 2 h before anaesthesia. General anaesthesia was induced with 0.2 µg.kg\(^{-1}\) sufentanil followed by 2 mg.kg\(^{-1}\) propofol and 0.5 mg.kg\(^{-1}\) atracurium to facilitate intubation of the patient’s trachea. Patient’s lungs were ventilated to normocapnia with 50% oxygen in air. Anaesthesia was maintained with sufentanil (0.2 µg.kg.h\(^{-1}\)) and sevoflurane at an initial end-tidal concentration of 1 minimum alveolar concentration, adjusted by age. Sufentanil was then maintained at a rate sufficient to maintain heart rate within 15% of the baseline value and systolic arterial blood pressure within 20% of the baseline value (using steps of ± 0.05 µg.kg\(^{-1}.h^{-1}\)). Sufentanil was stopped 30 min before the end of surgery. The patient’s trachea was extubated when they responded to verbal commands, were breathing spontaneously at a rate of at least 12 breaths.min\(^{-1}\), with end-tidal carbon dioxide partial pressure less than 6 kPA. Patients were admit-
Postoperative analgesia was provided by intravenous patient-controlled morphine. No other analgesia was given. Morphine was given intravenously every 5 min while the respiration rate was at least 10 breaths min⁻¹, the sedation score was ≤ 1 and the pain score was > 3. Patients less than 65 years of age were given 3-mg boluses of morphine, whereas older patients were given 2 mg. Once the pain scores were ≤ 3, patients were connected to the patient-controlled analgesia system set to deliver 1 mg morphine as an intravenous bolus with a 5-min lockout interval; a background infusion was not used. Patient-controlled analgesia was discontinued 48 h after surgery, and further analgesia was provided by combination of paracetamol, non-steroidal anti-inflammatory drugs and oral opioid as needed.

The cumulative dose of morphine given postoperatively (the sum of the amount titrated in the recovery room and patient-controlled analgesia over 48 h postoperatively) was recorded. Pain intensity was recorded at rest (in the recovery room and then 2, 6, 12, 24, 36 and 48 h after surgery) and during hip flexion (on the first and second postoperative mornings).

The incidence of opioid-related side-effects was recorded including nausea and vomiting, sedation (using the scale describe above), voiding difficulties, urinary retention and pruritus. Similarly, side-effects potentially related to ketamine and pregabalin were recorded, including hallucinations, nightmares and dizziness. Side-effects were defined as present when at least one episode was noted during the first 48 h after surgery.

During their pre-operative anaesthetic evaluation, patients were instructed in the use of quantitative sensory tests (pressure pain detection thresholds). These measurements were performed before surgery, then on the morning of the first and on the second day after surgery using a previously described method [16]. The area of mechanical secondary hyperalgesia to von Frey hair stimulation around the surgical wound was assessed with 60- and 100-g von Frey hairs (Bioseb In Vivo Research Instruments, http://www.bioseb.com). Hyperalgesia was determined by stimulating along three linear paths above and at right angles to the top, middle and bottom sides of the surgical incision in steps of 5 mm at 1-s intervals, starting well outside the hyperalgesic area. Stimulations continued towards the incision until patients reported the stimulation as being ‘painful’, ‘sore’, or ‘sharp’. The distance (in mm) from the incision to where sensations changed was measured, and a sum of the three assessments (top, middle and bottom) on the first and second postoperative days was calculated and used for statistical comparison [16]. If no change in sensation occurred, the stimulation was stopped 5 mm from the incision.

A handheld electronic pressure algometer (Somedic AB, Stockholm, Sweden) with a 0.5-cm² probe area was used to determine pressure pain detection threshold. The patients were instructed to activate a push button immediately on perception of pain, freezing the digital display. The average of three measurements with an inter-stimulus interval of 60 s was defined as pressure pain threshold value, expressed in kPa. Pressure pain thresholds were measured at 2–3 cm from the incision and on the opposite thigh the day before surgery and on the first and second postoperative days.

An intention-to-treat analysis was performed. The primary outcome was total morphine consumption over the initial 48 h postoperatively. Secondary outcomes included morphine titration given in the recovery room, numerical scale pain score at rest and on movement during the 2 days after surgery, pressure pain threshold, extent of hyperalgesia and side-effects. The primary endpoint was total morphine consumption during the first 48 h postoperatively. A clinically important morphine-sparing effect was considered to be 15 mg over 48 h. According to previous data (mean (SD) 46 (18) mg) [16] and for an α risk of 0.05 with a power of 80%, 25 patients per group were necessary. To account for drop-outs, we planned to include at least 28 patients per group. Since patients lost to follow-up were more numerous than planned, we enrolled a total of 142 patients at the Raymond Poin-
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caré and Ambroise Paré hospitals with local randomisation lists. The study began in September 2009 and ended in June 2011.

Continuous variables such as total 48-h morphine use, morphine titration in the recovery room, pressure pain thresholds and area of hyperalgesic pain threshold were compared with a factorial ANOVA with analysis of the ketamine and pregabalin factors and their interaction. Numerical scale pain scores were analysed by two-way ANOVA for repeated measures, followed by PLSD Fisher’s protected least significant difference test. Categorical data such as sex and incidence of side-effects were analysed with chi-square tests. Statistical analysis was performed with Statview for Windows (version 5.0; SAS Institute Inc, Cary, NC, USA); a value of $p < 0.05$ was considered statistically significant.

**Results**

Of 142 patients included, 120 patients had complete datasets, including the primary outcome (Fig. 1). An intention-to-treat analysis was performed on all 142 included patients. The patient and surgical characteristics for each of the four treatment groups are presented in Table 1.

Mean (SD) total 48-h morphine use was significantly reduced in the ketamine-alone group (52 (22) mg) and pregabalin-alone group (44 (20) mg) compared with the placebo group (77 (36) mg), $p < 0.001$. Total 48-h morphine use was also reduced in the combined ketamine and pregabalin group (38 (19) mg). A significant interaction between the groups that received pregabalin and the groups that received ketamine was observed ($p = 0.028$). Compared with the placebo group (25 (8) mg), morphine titration in the recovery room was significantly lower with pregabalin alone (18 (7) mg, $p = 0.01$), but not significantly reduced by ketamine alone (20 (7) mg, $p = 0.18$), with a significant interaction between ketamine and pregabalin ($p = 0.018$).

The pain scores at rest and on movement were similar in all groups at 24 and 48 h after surgery.

**Figure 1** Flow chart showing movement of patients through the study.
The incidence of side-effects was similar in all groups (Table 3). Patients experienced severe pressure alldynia on the surgical side. Pressure-induced pain thresholds were similar in each group. Patients developed a peri-incisional area of secondary hyperalgesia in the placebo group (451 (59) mm). No significant reduction in this area of secondary hyperalgesia was observed in the

### Table 1

Patients’ and surgical characteristics in patients receiving placebo, ketamine alone, pregabalin alone, and combined ketamine and pregabalin. Values are mean (SD), number or median (IQR [range]).

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 38)</th>
<th>Ketamine alone (n = 34)</th>
<th>Pregabalin alone (n = 35)</th>
<th>Ketamine and pregabalin (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>64 (11)</td>
<td>60 (17)</td>
<td>64 (9)</td>
<td>59 (12)</td>
</tr>
<tr>
<td>Sex; male/female</td>
<td>25/13</td>
<td>11/23</td>
<td>20/15</td>
<td>18/17</td>
</tr>
<tr>
<td>Weight; kg</td>
<td>78 (16)</td>
<td>75 (16)</td>
<td>77 (15)</td>
<td>79 (17)</td>
</tr>
<tr>
<td>Pre-operative pain at rest; NRS</td>
<td>2 (0–3 [0–7])</td>
<td>3 (0–3 [0–8])</td>
<td>3 (0–3 [0–10])</td>
<td>3 (0–4 [0–7])</td>
</tr>
<tr>
<td>Pre-operative pain on movement; NRS</td>
<td>5 (4–7 [0–8])</td>
<td>5 (3–6 [0–8])</td>
<td>5 (4–6 [0–8])</td>
<td>6 (4–7 [0–8])</td>
</tr>
<tr>
<td>Duration of surgery; min</td>
<td>102 (25)</td>
<td>112 (30)</td>
<td>103 (18)</td>
<td>103 (25)</td>
</tr>
<tr>
<td>Sufentanil consumption; µg</td>
<td>45 (10)</td>
<td>41 (11)</td>
<td>43 (11)</td>
<td>43 (11)</td>
</tr>
</tbody>
</table>

NRS, numerical rating scale (0: no pain to 10: worst possible pain).

### Table 2

Pain at rest and on movement in patients receiving placebo, ketamine alone, pregabalin alone, and ketamine and pregabalin. Values are median (IQR [range]).

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 38)</th>
<th>Ketamine alone (n = 34)</th>
<th>Pregabalin alone (n = 35)</th>
<th>Ketamine and pregabalin (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at rest in recovery room</td>
<td>7 (4–9 [0–10])</td>
<td>5 (2–8 [0–10])</td>
<td>5 (4–7 [0–10])</td>
<td>6 (3–8 [0–10])</td>
</tr>
<tr>
<td>Pain at rest at 24 h</td>
<td>2 (1–4 [0–6])</td>
<td>3 (2–4 [0–7])</td>
<td>3 (1–5 [0–6])</td>
<td>3 (1–4 [0–7])</td>
</tr>
<tr>
<td>Pain at rest at 48 h</td>
<td>3 (0–4 [0–6])</td>
<td>2 (0–3 [0–5])</td>
<td>2 (0–3 [0–5])</td>
<td>1.5 (0–3 [0–4])</td>
</tr>
<tr>
<td>Pain on movement at 24 h</td>
<td>5 (3–6 [0–10])</td>
<td>5 (4–6 [4–10])</td>
<td>5 (4–6 [0–9])</td>
<td>5 (4–7 [2–10])</td>
</tr>
<tr>
<td>Pain on movement at 48 h</td>
<td>5 (3–6 [0–8])</td>
<td>4 (3–6 [2–7])</td>
<td>5 (3–6 [1–7])</td>
<td>4 (3–5 [2–10])</td>
</tr>
</tbody>
</table>

NRS, numerical rating scale (0: no pain to 10: worst possible pain).

### Table 3

Incidence of side-effects over two postoperative days in patients receiving placebo, ketamine alone, pregabalin alone, and ketamine and pregabalin. Values are number (proportion).

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 38)</th>
<th>Ketamine alone (n = 34)</th>
<th>Pregabalin alone (n = 35)</th>
<th>Ketamine and pregabalin (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6 (16%)</td>
<td>6 (18%)</td>
<td>2 (6%)</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (5%)</td>
<td>4 (12%)</td>
<td>5 (14%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>PONV</td>
<td>6 (16%)</td>
<td>6 (18%)</td>
<td>6 (17%)</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Sedation score &gt; 2</td>
<td>2 (5%)</td>
<td>3 (9%)</td>
<td>5 (14%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (5%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (5%)</td>
<td>0</td>
<td>6 (17%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Nightmare</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Voiding difficulties</td>
<td>5 (13%)</td>
<td>8 (24%)</td>
<td>7 (20%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>5 (13%)</td>
<td>7 (21%)</td>
<td>7 (20%)</td>
<td>3 (9%)</td>
</tr>
</tbody>
</table>

Side-effects were defined as present when at least one episode was noted during the first 48 h after surgery.

Sedation was scored as 0 = no sedation; 1 = intermittent drowsiness; 2 = patient drowsy, but arousable to verbal stimulus; 3 = impossible to arouse verbally.

There were no significant differences between groups.

PONV, postoperative nausea and vomiting.

(Table 2). The incidence of side-effects was similar in all groups (Table 3).
pregabalin-alone group (441 (51) mm; p = 0.37). The area of secondary hyperalgesia was significantly reduced in the ketamine-alone group (318 (59) mm; p = 0.02) with no significant interaction between ketamine and pregabalin (combined ketamine and pregabalin group, 234 (42) mm; p = 0.49).

Discussion

This is the first clinical study to evaluate the combination of pre-operative pregabalin and intra-operative administration of ketamine for surgical patients scheduled for total hip arthroplasty. The combination induced a limited additional opioid-sparing effect but had no impact on acute pain or opioid-related side-effects. Ketamine reduced the area of secondary hyperalgesia around the surgical incision.

The two main goals of balanced analgesia are to improve analgesia and reduce side-effects. Quantitative reviews have suggested limited or no benefit of pregabalin for acute pain [12, 17] and a significant reduction in pain intensity with ketamine for 24 h after surgery [3, 5]. In our study, ketamine or pregabalin alone, or the combination of the two, did not influence acute pain scores after surgery. However, each drug and the combination produced a statistically significant and clinically important morphine-sparing effect. In fact, we observed a 37% reduction in total 48-h morphine use (26 mg) in the ketamine-only group, which is similar to the morphine-sparing effect reported previously [5]. Benefit in patients given pregabalin alone was similar. Interestingly though, the combination of pregabalin and ketamine only slightly further enhanced morphine sparing over 48 h.

This additional morphine-sparing effect seen with the ketamine and pregabalin combination was not sufficient to offer a reduction in the incidence of opioid-related side-effects, suggesting limited clinical benefit. Opioid sparing itself has no clinical value without reduction in opioid-related side-effects [18]. In addition, hallucinations have been described with ketamine [5] and sedation and dizziness with pregabalin [12]. However, the number needed to harm for hallucinations was estimated to be 286 when ketamine was administered during anaesthesia and our study was not adequately powered to detect such an incidence [5]. Our pregabalin dose of 150 mg is in the range (75–300 mg) of those commonly used in eligible studies of the review describing cognitive sedation and dizziness related to pregabalin use [12, 17]. Since our study was not adequately powered, we cannot exclude the possibility of additional side-effects related to the combination of ketamine and pregabalin.

Ketamine has been shown to have an effect on secondary hyperalgesia in several surgical models since the 1990s [1, 4, 6, 7]. We have confirmed the reduction in secondary hyperalgesia with ketamine. Our study offers the first clinical description of the absence of impact of pregabalin on secondary hyperalgesia after surgery. These data are in accord with a recent experimental study in volunteers and animals, where ketamine but not pregabalin reduced central sensitisation [19]. Our study did not find an additive antihyperalgesic effect of ketamine and pregabalin similar to that described in recent experimental study using opioid-induced hyperalgesia in rats [14].

In summary, pregabalin and ketamine each substantially reduce opioid consumption after total hip arthroplasty. Their combination is only slightly more effective than either drug alone. Ketamine seems to reduce secondary hyperalgesia with additional impact of pregabalin. However, the combination of ketamine and pregabalin does not allow reduction in morphine-related side-effects or pain intensity. Our results suggest that the small clinical impact of this combination does not presently support its recommendation in patients scheduled for total hip arthroplasty.

Competing interests

No external funding or competing interests declared.

References


