Wound infiltration with 1% pethidine provides an opioid-sparing effect after un cemented total hip arthroplasty: a prospective randomized study

Adela Hilda Onuțu1, Ioana Maria Iacob1, A. Todor2, D.O. Lucaciu2, I. Acalovschi3

1 Department of Anaesthesia and Intensive Care, Orthopaedic and Traumatology Clinic, Cluj-Napoca
2 Department of Orthopaedic and Traumatology, University of Medicine and Pharmacy “Iuliu Hațieganu”, Cluj-Napoca
3 Department of Anaesthesia and Intensive Care, University of Medicine and Pharmacy “Iuliu Hațieganu”, Cluj-Napoca

Abstract

Objective. Pethidine is a synthetic opioid also effective as local anesthetic, by blocking voltage-dependent sodium channels. Studies investigating pethidine efficacy providing anesthesia and analgesia in spinal, epidural, intravenous regional anesthesia and intraarticular administration showed good quality, intermediate duration, postoperative analgesia. We hypothesized that wound infiltration with 1%, 1 mg/kg pethidine, after un cemented total hip arthroplasty would be beneficial in a multimodal analgesic regimen.

Methods. This study compared two groups of consecutive patients, scheduled for un cemented primary total hip arthroplasty. Patients were randomized as follows: group WI (n = 19) who received wound infiltration, at the end of surgery, with 1%, 1 mg/kg pethidine, and group IM (n = 19) who received 5%, 1 mg/kg pethidine intramuscular injection, immediate after wound closure. All surgeries were done under spinal anesthesia with 15 mg, 0.5% bupivacaine. After surgery a standard analgesic protocol was started with 1 g acethaminophen, per os, intravenous 30 mg ketorolac, every 8 hours and morphine with a patient-controlled analgesia pump, for 24 hours. Study endpoints were: 24-hour total morphine consumption and pain scores on a numerical rating scale (NRS) at active movement of the operated leg, at 6 and 12 postoperative hours.

Results. Recorded 24-hour total morphine consumption was significantly lower in group WI (4.6 ± 1.3 mg vs 9.3 ± 0.9 mg). Group WI showed a significant reduction in the postoperative NRS pain score at movement at 6 hours, median score (range) 5 (4-7) vs 6 (5-7) (p < 0.005) for the IM group, with no further differences between groups.

Conclusions. Wound infiltration with 1%, 1 mg/kg pethidine, after un cemented total hip arthroplasty reduced the postoperative 24-hour total morphine consumption and provided analgesia for the first six postoperative hours in a multimodal analgesic regimen.

Keywords: analgesia, arthroplasty, hip, infiltration, wound, pethidine

Introduction

Pethidine is a synthetic opioid that is known to have peripheral effects on opioid receptors [1]. Additionally, pethidine has local anesthetic properties and blocks voltage-dependent sodium channels [2]. Opioid recep-
wound infiltration with appropriate drugs could prevent central sensitization, and could be effective in chronic postoperative pain prevention [11, 12]. However, there is not enough evidence for LIA to be recommended as part of PROSPECT (Procedure specific postoperative pain management working group) guidelines, for postoperative analgesic management after total hip arthroplasty (THA), under spinal anesthesia. The endpoints of the study included: the 24-hour total morphine consumption and the intensity of pain at movement, evaluated with numerical rating scale (NRS) at 6 and 12 postoperative hours.

Methods

After University Ethics Committee approval [University of Medicine and Pharmacy “Iuliu Hațieganu” Cluj-Napoca, Romania, nr: 331/2011], 38 patients ASA I-II, aged between 40-65 years, scheduled for primary uncemented THA consented for enrolment in the study. Osteoarthritis represented main indication for hip joint replacement. Patients with chronic hepatic illness, chronic renal illness, coagulation abnormalities, severe diabetes, history of peptic ulcer, known allergy to local anesthetics, morphine, pethidine or nonsteroidal anti-inflammatory drugs, obese patients (BMI > 25), those with peripheral neurologic or psychiatric disorders and those patients unable to use the patient-controlled analgesia (PCA) pump were excluded from the study. Patients with significant alcohol or opioid medication abuse were also excluded.

Patients were recruited the day before surgery, on the surgical ward. After written informed consent was obtained, patients were randomly assigned, by a physician not involved in the study (sealed envelope method), into one of two study groups: group WI (wound infiltration) (n = 19) and group IM (intramuscular injection) (n = 19). After surgical wound closure, patients in group WI received wound infiltration with 1% pethidine (1 mg/kg total dose), while patients in group IM received an intramuscular injection of 5% pethidine (1 mg/kg total dose). Preoperatively, patients were instructed on the appropriate use of the PCA pump, and were oriented to evaluation of pain intensity using an 11-digit numerical rating scale (NRS, bounded by 0 = no pain, and 10 = worst pain).

After arrival in the operating theatre, a 16-gauge intravenous catheter was placed into a vein of the distal arm, patients received premedication with 0.03 mg/kg midazolam i.v., 15 min before surgery, and a saline solution infusion was started. All patients received spinal anesthesia with 0.5% 15 mg plain bupivacaine (Marcain®, Astra-Zeneca, Sweden), at the L2-L3 intervertebral space, using pencil point needles (25- or 27-gauge), with the patient in sitting or lateral decubitus position. Immediately after the spinal injection, all patients were placed supine and prepared for surgery, which was performed with the patient in the supine position. Standard noninvasive monitoring consisted of continuous electrocardiogram (ECG), peripheral pulse oximetry and automatic noninvasive blood pressure measurement with Infinity® Vista XL, Draeger Medical Systems, Inc. (Telford, PA, USA) monitor. Cementless total hip replacement was performed by the same surgical team using Hardinge direct lateral approach [13], with Trilogy acetabular component (Zimmer, Inc., Warsaw, Poland) and Versys Fiber Metal Taper stem (Zimmer, Inc., Warsaw, Poland). In all cases polyethylene liners and cobalt-chromium heads were used. A deep, passive drain was placed in each case, and was removed after the first 24 postoperative hours. All patients received oxygen from a face mask with a flow rate of 4 l/min, for all the duration of surgery.

After surgical closure, for patients in group WI, the surgeon was asked to infiltrate the wound (subcutaneously) with 1% (total of 1 mg/kg) preservative-free pethidine solution (Mialgin®, Zentiva S.A., Bucharest, Romania). The infiltration was performed along the incision with separate injections, with the needle (22 gauge, 50 mm) being inserted every 3 cm, at a 45 degree angle to the skin. After needle insertion, infiltration of the subcutaneous tissue was made in a fan-like manner, while the needle was withdrawn.

Patients in group IM received, immediately after wound closure, 5% (total of 1 mg/kg) pethidine solution (Mialgin®, Zentiva S.A., Bucharest, Romania) intraglutally, in the opposite (unoperated) leg.

After surgery, all patients were transferred in the post anesthesia care unit (PACU), where they remained for 24 hours. Monitoring included: ECG, noninvasive blood pressure, peripheral pulse oximetry, temperature, urinary output, pain, signs of infection and blood loss. Immediately after patient arrival, a multimodal analgesic regimen was begun, consisting of 1 g acetaminophen p.o. (Paracetamol®, Europharm SA, Brasov, Romania) and 30 mg ketorolac i.v. (Ketorol®, Dr. Reddy’s Laboratories Ltd, Slough, UK) every 8 hours. Subsequently, patients were given access to a PCA pump (BBraun®, Melsungen, Germany) with 1% morphine (Morfina®, Zentiva S.A., Bucharest, Romania), (1 mg/ml). The pump was set to deliver a 1 mg bolus of morphine i.v. with a lock-out period of 10 minutes, 4-hour limit 24 mg and without a continuous background infusion. All patients were given humidified
Wound infiltration analgesia with 1% pethidine oxygen on nasal prongs with a flow rate of 4 l/min, for 24 hours. The time to first i.v. morphine bolus through the PCA pump, total number of attempts and total morphine consumption were recorded. The PCA morphine administration was stopped at 24 hours, when patients were transferred to the surgical ward. In our institution patients do not receive morphine PCA on the surgical ward because of lack of nursing in service for PCA. At 6 and 12 hours postoperatively, we recorded NRS pain scores with movement of the operated leg, while patients were asked to elevate the leg to 45 degrees, thus involving contraction of the quadriceps muscle. Flexion of the knee to 90 degrees was also permitted. Patients were instructed to maintain resting pain score NRS < 4 by using the morphine PCA pump. In our institution, patients with total hip arthroplasty are not allowed to stand or walk during the first 24 postoperative hours.

Side effects (nausea, vomiting, pruritus, respiratory depression) were also recorded. Medical staff involved in patient management and in PACU data collection, were blinded to the study group to which patients had been assigned.

The primary outcome of the study was postoperative 24-hour total morphine consumption, as this was measured by recording the amount of morphine used with PCA device, and we considered a 50% reduction of this value to be clinically important. With alpha set at 0.05 we calculated, post hoc, a statistical power of 70%, for our study.

Group data were presented as mean ± standard deviation (SD) and median (range). Parametric data were analyzed using Student’s t test. Two-sample Mann-Whitney U test was used to compare groups for primary and secondary outcomes. We considered p < 0.05 to be statistically significant.

Results

Study groups were comparable for baseline characteristics (age, gender, weight, height), and also, for surgery duration and position for spinal anesthesia (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Demographic data and duration of surgery</th>
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<tbody>
<tr>
<td>WI* group (n = 18)</td>
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<tr>
<td>-------------------</td>
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<tr>
<td>Age, yr.</td>
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<tr>
<td>Male/Female</td>
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<tr>
<td>Weight, kg</td>
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<td>Height, cm</td>
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<tr>
<td>Duration of surgery, min</td>
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<td>Position for spinal, sitting/lateral</td>
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* wound infiltration group; ** intramuscular group values are expressed as mean (standard deviation)

Thirty six patients finished the study procedures as two patients were excluded, one in each group because of protocol violations in the PCA pump use (Fig. 1).
The mean value of the 24-hour total morphine consumption was significantly lower in the WI group as compared with the IM group. Time to first postoperative i.v. morphine bolus was significantly longer in group WI compared with group IM (Table 2).

Table 2. Postoperative 24-hour total morphine consumption, NRS pain scores at movement and the time to first morphine bolus

<table>
<thead>
<tr>
<th></th>
<th>WI* group (n = 18)</th>
<th>IM** group (n = 18)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h morphine consumption, mg</td>
<td>4.6 (1.3)</td>
<td>9.3 (0.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NRS 6†</td>
<td>5 (4-7)</td>
<td>6 (5-7)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>NRS 12†</td>
<td>7 (6-8)</td>
<td>7 (6-8)</td>
<td>1</td>
</tr>
<tr>
<td>Time to first morphine bolus, min</td>
<td>257 (52)</td>
<td>160 (30)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* wound infiltration group; ** intramuscular group
† values are expressed as mean (standard deviation)
‡ numerical rating pain score at 6 postoperative hours – values are expressed as median (range)
§ numerical rating score at 12 postoperative hours – values are expressed as median (range)

Median pain score, NRS rated, at 6 postoperative hours was significantly lower in WI study group. We found that pain NRS scores, in the “middle fifty” of the range, were higher than or equal to the median value of 5, in WI group. We also observed that 75% of all patients in group WI had lower pain scores than the median value of the IM group (Fig. 2). Referring to the IM group pain scores, at six postoperative hours, we noted that interquartile range equals 0, meaning that all values of the middle fifty equals the median value of 6, showing a homogenous, higher intensity of pain with movement, in this group. At 12 postoperative NRS pain scores with movement showed no difference between groups.

A similar number of patients developed nausea and vomiting in PACU (Table 3). Two patients in WI group and 3 patients in group IM required antiemetic treatment for vomiting.

Table 3. Side effects

<table>
<thead>
<tr>
<th></th>
<th>WI* group (n = 18)</th>
<th>IM** group (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (n)</td>
<td>6 (33%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Vomiting (n)</td>
<td>3 (16%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Pruritus (n)</td>
<td>3 (16%)</td>
<td>0</td>
</tr>
</tbody>
</table>

* wound infiltration group; ** intramuscular group
values are expressed as number of patients (n [incidence, %])

Fig. 2. Box plots of NRS pain scores, with movement at 6 and 12 postoperative hours, for both study groups. Data are presented as median NRS with 25th to 75th percentiles (box) and range (whiskers), (NRS – numerical rating scale, WI – wound infiltration group, IM – intramuscular group)

Minor pruritus was recorded in 3 (16%) cases, only in WI group.

During hospitalization no wound infection was seen in any patient involved in this study.
Discussion

Proper management of the acute postoperative pain may prevent chronic pain after THA [12]. Infiltration of the wound with local anesthetics provides analgesia by blocking the transmission of pain due to the action on voltage-dependent sodium channels within the axon membrane. Local anesthetics may also reduce the release of inflammatory mediators responsible for pain and hyperalgesia by sensitization of nociceptive receptors [14].

There are a few studies concerning the efficacy of LIA in patients with THA. Andersen et al. [15] compared LIA analgesia with a solution consisting of ropivacaine, ketorolac and epinephrine, to a control group receiving infiltration with saline solution (placebo). Patients in the treated group had less pain up to 2 weeks postoperatively and a better outcome. In a recent controlled trial, Lunn et al. [16] with a high-volume LIA with ropivacaine 0.2% technique showed postoperative NRS pain scores at movement lower than those we found in our study. In a review by Kehlet and Andersen [17] the conclusion was that existing data do not support local infiltration analgesia for hip replacement, as long as a multimodal oral nonopioid analgesic was provided. However, in many previous studies wound infiltration analgesia showed a safety profile and an opioid sparing effect in joint replacement surgery [18, 19].

We hypothesized that wound infiltration analgesia using pethidine would prove an postoperative analgesic effect, by a peripheral mechanism by exerting a double antinociceptive effect in the wound area (by blocking voltage-depending sodium channels on the nerve endings and also by interacting with mu and delta opioid receptors on neutrophils, immunocytes and keratinocytes). LIA with pethidine could be more effective in the treatment of postoperative acute pain, in a multimodal analgesic protocol. For this reason, we used 1 mg/kg of 1% pethidine, the minimum effective concentration which acts as local anaesthetic [5]. Our hypothesis is supported by studies that have demonstrated the analgesic effect of opioids applied on peripheral nerves by reducing the amplitude of the action potentials in sensory fibers (type C) [20, 21].

In an experimental murine model, Clark et al. [22] studied the effect of preincisional infiltration of wound area with morphine in different doses. They showed that preincisional wound infiltration with morphine, in low doses, reduced wound area cytokines productions, but the effect was insufficient to reduce acute pain. In the same study, in larger doses, morphine mediated reduction in wound area neutrophil presence and authors concluded that this fact could affect the wound healing process and lead to wound infections.

Zajaczkowska et al. [23] studied the effects of preincisional wound infiltration with morphine, bupivacaine and combination of these two substances, at the trocar entry sites for laparoscopic cholecystectomy. They found that pain intensity and total tramadol requirement, as rescue analgesia, were lower in the study groups, but not statistically significant versus control. However, the time from completion of surgery to the first analgesic requirement was significantly longer in the patients with wound infiltration with morphine, bupivacaine and the combination of these substances. Authors concluded that preincisional, opioid and local anesthetic, infiltration at trocar insertion sites has a doubtful clinical relevance as the favorable effect failed to reach statistical significance.

Fentanyl was also found to enhance analgesia by peripheral mechanism. Added to lidocaine for wound infiltration decreased the intensity and movement-associated postoperative pain [24]. However, postsurgical ropivacaine infiltration, with or without adding fentanyl, demonstrated no differences in postoperative pain relief compared to a balanced general anesthesia including i.v. fentanyl [25].

Khajavi et al. [26] investigated the efficacy of subcutaneous infiltration of the wound with tramadol following pyelolithotomy versus i.v. administration of tramadol. They found a reduced opioid consumption and less nausea and vomiting. The average time to the first pethidine requirement, as rescue analgesia, was longer in the subcutaneous group 45 ± 8 min vs 21 ± 12 min in the intravenous group. In this study, tramadol analgesia could be the consequence to a systemic effect following the absorption of the drug. However, administration of 0.25% tramadol solution containing 100 mg tramadol, as sole agent, was not effective for intravenous regional anaesthesia [27]. In our study after wound infiltration with 1% pethidine, associated with a postoperative multimodal analgesic regimen, the analgesic effect was much longer, 257(52) min, to the first morphine requirement as rescue analgesia.

In the only study that investigated the influence of wound infiltration with 50 mg pethidine on postoperative pain after laparoscopic tubal ligation, the authors did not find any effect on postoperative pain or recovery [28]. However, they considered that pain from other areas might have masked any local analgesic effect. The visceral and the referred pain related to this surgical procedure were probably more significant that the parietal pain from wound at the trocar insertion sites.

In our study on patients with THA the wound infiltration with pethidine was more effective although the surgical intervention was more extensive. We obtained a significantly longer period to the first analgesic requirement, a significantly lower overall morphine
consumption for the first 24 postoperative hours, and a significant reduction in pain intensity 6 hours postoperatively in comparison with IM group. The analgesic effect could be considered peripheral in origin, as the controlled group of patients received an equivalent dose of pethidine intraglutally in the opposite leg. The different results of the two studies could be explained by the difference in the concentration of the pethidine solution, used: 1% pethidine solution in our study and 0.5% pethidine solution in the former study.

Pethidine was also effective when added in small amount to a local anesthetic solution. In children, infiltration of the surgical bed after tonsillectomy with a mixture of pethidine and 2% lidocaine prolonged the pain relief postoperatively and reduced the need for postoperative analgesics [29].

In our study a significant number of patients in both groups developed nausea and/or vomiting postoperatively. This side effect is probably due to the action of both opioids we used, pethidine and morphine, on the chemoreceptor trigger zone. Even if the 24-hour total morphine consumption was significantly reduced in WI group, the incidence of nausea and/or vomiting was still increased compared with the IM group.

This study has several limitations. All patients involved in the study complained of preoperative pain, but a record of WOMAC (Western Ontario and McMaster University Osteoarthritis Index) would have added important information about the severity of pain. WOMAC is an index used in patients with osteoarthritis of the hip and knee, to assess secondary pain, joint stiffness and psychosocial disability. This index is derived from a questionnaire that uses 24 parameters and that can be used to monitor the course of the disease [30]. Another limitation is that we did not consider in our analysis the extent of the surgical incision, which may affect pain intensity and/or duration. However, all surgeries were performed by the same surgical team so it is unlikely that the surgical exposure would have been significantly different between the 2 patient groups. It is also possible that the analgesic solution was not distributed uniformly in the subcutaneous tissue, and there could have been some leakage of the infiltrating solution outside the wound in some of our patients, diminishing the analgesic effect. However, the same infiltration technique was used by the same surgeon in all patients, so it is unlikely that the infiltration technique would have been systematically different in WI group.

Also, the spinal anesthesia was done using two different positions (sitting and lateral position) and assuming that plain 0.5% bupivacaine is slightly hypobaric, this could have affected the level and duration of anesthesia and analgesia. Since all patients were placed in the supine position immediately after the spinal injection, it is unlikely that the spread of the intrathecal local anesthetic would have differed in the two patient groups.

There might be concerns regarding the postoperative oral administration of acetaminophen. Acetaminophen is a high lipophilic drug and it has been proven to have a rapid absorption, by passive transport, from the small bowel; it is thus unlikely that the oral route would have differed between the groups or that the postoperative absorption would have been different from the preoperative absorption [31]. We used this route of administration of acetaminophen postoperatively for economical reasons, and we accept the fact that in some of our patients who experienced vomiting, the availability of the drug was diminished. This may be a limitation, since absorption may have been variable; however, a similar number of patients in each group (3 patients and 5 patients) experienced vomiting postoperatively, so this should be only a minor concern.

Pain after THA has a complex nociceptive triggering mechanism that combines the wound site, the profound soft tissues, bones and also the painful stimuli determined by the tonic contractions of quadriceps muscle occurring in the first 12 postoperative hours, as a consequence of the manipulation of the operated leg during hip displacement and surgical procedures. Wound infiltration in THA interferes only with a part of this complex mechanism.

In conclusion, wound infiltration with 1 mg/kg, 1% pethidine, as part of multimodal analgesia after THA under spinal anesthesia, reduced the first 24-hour total morphine consumption and provided analgesia for the first 6 postoperative hours. Our study suggests that wound infiltration with 1% pethidine can be a useful adjunctive tool in the postoperative analgesic management of THA, and it requires further investigation.

Acknowledgement
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Conflict of interest
Nothing to declare

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Infiltrația plăgii cu pethidină 1% determină reducerea consumului de opioid după artroplastia totală necimentată de șold: un studiu prospectiv randomizat

Rezumat

Introducere. Petidina este, după cum se știe, un opioid care acționează și ca anestezic local, prin blocarea canalilor de sodiu voltaj-dependente. Numeroase studii care au investigat eficacitatea anestezică și analgezică a petidinei în administrare spinală, peridurală, intravenoasă regională și intraarticulară au arătat că petidina determină o analgezie postoperatorie de bună calitate și de durată intermediară. Am pornit de la ipoteza că inflația plăgii operatorii cu 1 mg/kg petidină 1%, în artroplastia totală necimentată de șold, ar putea avea un efect benefic într-un regim multimodal de analgezie postoperatorie.

Pacienții și metodă. Acest studiu a comparat două grupuri de pacienți care au fost supuși consecutiv artroplastiei totale primare necimentate de șold. Pacienții au fost randomizați după cum urmează: grupul WI (n = 19) la care s-a realizat inflația plăgii cu 1 mg/kg, petidină 1% la sfârșitul intervenției chirurgicale și grupul IM (n = 19) la care s-a administrat 1 mg/kg, petidină 5% intramuscular, imediat după închiderea plăgii chirurgicale. Toate intervențiile chirurgicale s-au...
desfășurat în anestezie spinală cu 15 mg bupivacaină 0,5%. Postoperator, protocolul de analgezie a cuprinzat acetaminofen 1 g, per os și 30 mg ketorolac, intravenos, la 8 ore interval, la care s-a adăugat analgezie controlată de pacient, cu morfina. S-au urmărit: consumul total de morfină în primele 24 de ore postoperator și scorurile de durere, pe scala numerică, la mobilizarea postoperatorie a membrului operat la 6 și 12 ore postoperator.

Rezultate. Consumul total postoperator de morfină, în primele 24 de ore, a fost semnificativ scăzut în grupul WI (4,6 ± 1,3 mg vs 9,3 ± 0,9 mg). Scorurile de durere, la mobilizare la 6 ore postoperator, în grupul WI au fost semnificativ reduse față de cele din grupul IM, cu o mediană de 5 (4-7) vs 6 (5-7) (p < 0,005), fără a se mai înregistra diferențe între grupuri la 12 ore postoperator.

Concluzii. Infilația plângii chirurgicale cu 1 mg/kg petidină 1% a redus consumul total de morfină postoperator, în primele 24 de ore și a determinat analgezie în primele 6 ore postoperator, într-un regim multimodal de analgezie.

Cuvinte cheie: analgezie, artroplastie, șold, infilație, plagă, petidină