Local analgesic Effect of Pethidine Infiltrated Intrafascially after Total Abdominal Hysterectomy: A Randomized, Double-Blind Study

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Abstract

Objective: Surgical-site infiltration with local anesthetics is a key component of multimodal analgesia regimen for adequate postoperative pain management. This randomized, double-blind study was designed to evaluate the local analgesic efficacy of pethidine in patients undergoing total abdominal hysterectomy (TAH) through a Pfannenstiel incision. Materials and Methods: Patients were randomized into two groups. The first group received wound infiltration (WI) with 0.5 mg/kg pethidine, diluted in 15 ml normal saline, and injected in the fascial layer at the end of surgery, combined with a simultaneous intramuscular (IM) injection of 2.5 ml normal saline (WI group). The second group received WI with 15 ml normal saline combined with an IM injection of 0.5 mg/kg pethidine and diluted in 2.5 ml normal saline (IM group). All patients received general anesthesia following a standardized anesthetic protocol. Study end points were 24-h total morphine consumption and pain scores based on a visual analog scale (VAS) at rest and on coughing at 1, 3, 6, and 24 postoperative h, as well as sedation scores observed using a 0–10 numeric rating scale. Adverse effects from morphine uptake, such as nausea, vomiting, and the need for rescue antiemetics, were recorded as well. Results: Postoperative VAS assessments showed no statistically significant advantage between WI and IM method, while the total (24h) consumption of morphine was lower in the IM, compared to the WI group (27.2%). The latter demonstrated a consistently higher median sedation score at all assessed time points after the operation ($P < 0.05$); however, it was significantly different only at the 6 h time point. Conclusions: Local WI with pethidine after TAH did not reduce the total morphine consumption for the first 24 h postoperatively. Morphine consumption was lower in the IM group, compared to the WI group. Further studies are needed to assess the effectiveness of pethidine as a local anesthetic agent.

Keywords: Pain management, pethidine, postoperative analgesia, total abdominal hysterectomy, wound infiltration

INTRODUCTION

Effective postoperative pain management still remains a major medical challenge for anesthetists. Total abdominal hysterectomy (TAH) is known to be associated with moderate-to-severe postoperative pain. Although epidural analgesia is considered to be the gold standard for major abdominal surgeries, less invasive methods could be employed in daily practice, especially when there are severe contraindications for applying these techniques. Specifically, local infiltration analgesia as a part of a multimodal postoperative analgesic regimen remains a simple and inexpensive technique used across multiple surgical specialties to reduce opioid consumption and enhance patients’ recovery and rehabilitation.

Pethidine (also known as meperidine) is a synthetic opioid of the phenylpiperidine class. It exerts its analgesic effects by acting as an agonist at the $\mu$-opioid receptors, but it has also antishivering effects through stimulation of $\kappa$-opioid receptors. In addition to these opioidergic properties, it has been proven to demonstrate a local anesthetic activity, which is mainly related to its interactions with voltage-dependent sodium-ion channels. Electrophysiological studies have shown that perineural injection of 1% pethidine blocked both sensory and motor conduction.

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motor conduction in a dose-related manner. The blocking effect of pethidine on peripheral nerve conduction has been evaluated both in vitro and in vivo animal studies.

Apart from local infiltration analgesia, pethidine is known to be effective through spinal or epidural route, in intravenous (IV) regional anesthesia, or even intra-articularly, as an alternative to local anesthetics in arthroscopy. Moreover, this technique could also prevent central sensitization by blocking nociceptive afferents and could be valuable for preventing chronic pain to arise after a major abdominal surgery. In addition to this, there is enough evidence that local infiltration analgesia is strongly recommended by Procedure-Specific Postoperative Pain Management Working Group in TAH (Grade A) for postoperative pain management.

This study was performed with the hypothesis that intrafascial wound infiltration (WI) with 0.5 mg/kg of pethidine exerts an opioid-sparing effect in patients undergoing TAH with salpingo-oophorectomy under general anesthesia. Primary outcome variables were pain intensity evaluated with visual analog scale (VAS) score at rest and on coughing at 1, 3, 6, and 24 postoperative h. The secondary variable was sedation after the effect of opioids, evaluated with a linear numerical scale of 0–10 at 1, 3, 6, and 24 postoperative h, as well as total morphine consumption. We also recorded the adverse effects of morphine such as nausea and vomiting.

**Materials and Methods**

This randomized study was carried out in our Department of Anaesthesiology and Pain Medicine, “Alexandra” General Hospital, Athens, Greece, over a period of 1-year duration (December 1, 2011–November 30, 2012), following approval from the Scientific Ethical Committee of our institution (reg. number: 20th theme, 5th Session, Approval Date: 11/5/2010).

Oral and written consent was obtained from sixty patients with the American Society of Anesthesiologists physical Status I-II, aged between 45 and 65 years, who were scheduled for TAH with salpingo-oophorectomy, under general anesthesia through a Pfannenstiel incision. Preoperatively, each patient was visited and instructed on the use of the IV patient-controlled analgesia (IV-PCA) pump and the use of the 0–10 VAS scale (bounded by 0 = no pain and 10 = worst imaginable pain). We decided to recruit this number of subjects based on previous studies performed in the field, following similar methodology. We have not performed power calculations before the study.

This study was designed in a double-blind, randomized manner. Randomization was obtained by computer-generated random numbers and ensured with a sealed envelope technique, which were opened at the end of the surgical procedure. A nurse who did not participate in the study was asked to prepare the diluted solutions for the two syringes mentioned below. Patients enrolled in the study were assigned into two study groups: WI group (n = 30) and intramuscular (IM) group (n = 30). After surgical wound closure, patients in WI group received 0.5 mg/kg of pethidine intrafascially, in a 15 ml saline syringe and a simultaneous IM injection of 2.5 ml of normal saline, whereas the IM group received an IM injection of 0.5 mg/kg intraglutentially in a solution of 2.5 ml and a simultaneous infiltration of 15 ml of normal saline intrafascially. The person who prepared the study drugs was blinded of the study and was not involved in data collection.

The exclusion criteria were malignancy, patients on chronic analgesic medications, such as selective serotonin reuptake inhibitors, anxiolytics, antiepileptics, antipsychotics, or exaggerated alcohol consumption (defined as drinking more than 1 drink/day for women and up to 2 drinks/day for men), as well as those with known allergy to local anesthetics, morphine, pethidine, or nonsteroidal anti-inflammatory drugs. Furthermore, those with chronic hepatic disease, chronic renal impairment, coagulation abnormalities and diabetes, as well as obese patients with body mass index >30 kg/m² were excluded from enrollment. Finally, patients having difficulty understanding Greek so unable to give consent and use the PCA pump were also omitted. After selection and randomization, ten patients were excluded because the surgeon decided to proceed with a midline vertical and not a Pfannenstiel incision, whereas during follow-up in the IM group, four patients were omitted due to reoperation.

All patients underwent a standard anesthetic protocol. They were premedicated with 3 mg of bromazepam and 150 mg of ranitidine, administered orally 12 h before the planned surgery; this is a routine procedure for our hospital. After arrival in the operating theater, a 17-gauge peripheral IV cannula was placed, and Ringer’s lactate solution infusion was initiated. General anesthesia was induced with 2.5 mg/kg of propofol and 100 μg of fentanyl. Tracheal intubation was facilitated by 0.6 mg/kg of rocuronium. Anesthesia was maintained by sevoflurane 2% and 50% nitrous oxide in oxygen.

Intraoperative monitoring included an electrocardiogram (leads II and V₅), noninvasive blood pressure (at 5 min intervals), pulse oximetry, capnography, end-tidal gas monitoring, and train-of-four stimulation. Sevoflurane concentration was adjusted to maintain adequate anesthesia depth as assessed clinically and age-related minimum alveolar concentration. The patients’ lungs were ventilated by intermittent positive pressure ventilation using a circle system to maintain normocapnia. The urinary bladder was catheterized. Perioperative fluid management was accomplished with the maintenance of Ringer’s lactate infusion, and transfusion was given if needed. Heart rate and mean arterial pressure were maintained within 20% of the preoperative value.

All patients received the same analgesia regimen intraoperatively, which included a total dose of 6 μg/kg fentanyl, as well as 40 mg of IV parecoxib and 1000 mg of IV acetaminophen, whereas ondansetron 0.1 mg/kg was
given ½ h before the completion of the surgery. At the end, residual neuromuscular block was reversed with neostigmine and atropine. Tracheal extubation was performed based on the standard criteria for extubation.

WI was performed by the primary surgeon who was blinded to the group assignment. After the closure of the fascia, for patients allocated in both groups, the surgeon was asked to infiltrate the wound with a 50 mm in length, 18-gauge needle. The infiltration was performed along the incision with separate injections, with the needle being inserted every 3 cm, at a 45° angle to the skin.

After having completely recovered in postanesthesia care unit, patients were transferred to the Gynecology Ward, where they were observed by the anesthesiologist, who was blinded to the group assignment, for 24 h. Total duration of the study was 24 h from the time of extubation. Pain score was assessed by VAS (0 = no pain and 100 = worst pain). Pain scores were recorded immediately after extubation (taken as 0 h) and after 1, 3, 6, and 24 h later, at rest and after cough, while sedation score was observed at the same hours.

Postoperative analgesia was provided with an IV-PCA pump with 0.5 mg/ml of morphine. The device was set to deliver a 1 mg bolus of morphine IV, with a lock-out period of 7 min, a 4 h limit of 24 mg morphine, and without a continuous background infusion. All patients were given humidified oxygen on nasal cannula with a flow rate of 2–4 l/min for 24 h.

The accumulated data were analyzed using Student’s t-test, two-way ANOVA (followed by Bonferroni correction), or Mann–Whitney U-test, where appropriate. Differences with \( P < 0.05 \) were considered as statistically significant.

**Results**

Study groups were comparable for baseline characteristics (age, gender, weight, and height) and also for type and duration of surgery [Table 1]. Forty-six patients finished the study procedures, while 14 were excluded from the study. Of the latter, ten were excluded because the surgeon decided to proceed with a vertical midline incision, and four of them either needed reoperation or did not comply with the criteria of our study [Figure 1].

The mean value of the 24 h total morphine consumption was significantly lower in the IM group as compared with the WI group (−27.2%; 11.33 ± 8.30 vs. 15.56 ± 9.69 mg, as mean ± SD, respectively). Moreover, the morphine consumption was consistently, but not significantly, lower in the IM group as compared to the WI group, at all examined time points (1 h: −29.3%; 3 h: −8.9%; 6 h: −19.3%; 24 h: −40.1%).

The VAS pain scores after cough [Figure 2] and at rest [Figure 3] demonstrated no significant differences between the two study groups. However, the median sedation scores achieved after the IM administration of pethidine were consistently lower than those after the administration of the drug through WI [Figure 4]. However, only at 6 hrs after the operation did the WI group exhibited a statistically significant higher sedation score (\( p < 0.05 \)), compared to the one reported for the IM group [Figure 4].

Finally, it should be noted that a similar number of patients developed nausea and vomiting in the gynecology ward and that all patients recovered well and were discharged, without any complications or wound infections (28% vs. 48%, 16% vs. 5% in WI group and IM group, respectively).

**Discussion**

This study investigates the analgesic effects of a meticulous surgical site infiltration technique with pethidine in patients undergoing TAH through a Pfannenstiel incision. According to pethidine pharmacokinetic principles, IM injection was considered to have a duration of action of at least 4–6 h. Our results indicate that compared to IM administration, postincisional subfascial wound infusion of pethidine does not provide better postoperative analgesia or decreased morphine consumption and lower pain scores in a statistically significant manner as reported in previous studies in relevant literature. One of the strengths of our study is that we included a well-recognized multimodal regimen, such as acetaminophen and parecoxib, in combination with an opioid with well-proven local anesthetic properties.[8,10,21]

Local infiltrative analgesia with local anesthetics is an established method of providing postoperative analgesia. It is suggested that the mechanism involved blocks the transmission of pain due to activation of voltage-dependent sodium channels,[9] and furthermore, sensitization of nociceptive receptors reduces the release of inflammatory mediators causing pain.[24,25] A recent study has shown the efficacy of WI during total abdominal hysterectomies, reducing the opioid requirements during the first postoperative 24 h,[26] and another one[27] has confirmed its suggested mechanism in abdominal surgeries using a neuroanatomical approach. Moreover, Jabalameli et al. found that subcutaneous administration of pethidine or tramadol, compared to bupivacaine, had an opioid-sparing effect after cesarean section.[28] Söderlund et al. featured pethidine as an effective alternative to local anesthetics during intra-articular administration in joint-knee surgery, and these results were consistent with a previous study of Ekblom et al. evaluating pain in arthroscopies comparing prilocaine to pethidine.[18,29] Moreover, apart from the efficacy

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**Table 1: Demographic data, duration, and type of surgery in the performed study**

<table>
<thead>
<tr>
<th></th>
<th>WI group (n=25)</th>
<th>IM group (n=21)</th>
<th>t-test comparison (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42.4 (7.9)</td>
<td>46.2 (10.2)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.8 (11.5)</td>
<td>67.3 (8.4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.4 (7.7)</td>
<td>161.9 (8.4)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Duration of the operation (h: min)</td>
<td>1:27 (0:28)</td>
<td>1:49 (0:45)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

WI: Wound infiltration, IM: Intramuscular
assessed for eligibility (n = 60)

EXCLUSION

Patients with allergies to pethidine, patients with a history of respiratory or cardiovascular disorders, and patients who had undergone elective surgery were excluded from the study.

ALLOCATION

Patients were randomized to either the wound infiltration (WI) group (n = 25) or the intramuscular (IM) group (n = 25).

FOLLOW-UP

Lost to follow-up (n = 0) or re-operation (n = 0) in the WI group, whereas the IM group had 0 patients lost to follow-up and 4 patients re-operated.

ANALYSIS

Analysis was conducted in the WI group (n = 25) and the IM group (n = 21).

Figure 1: Flowchart of the recruitment procedure followed, where patients in the wound infiltration group received pethidine infraspinally (0.5 mg/kg in a 15 ml saline syringe and a simultaneous intramuscular injection of 2.5 ml of normal saline), whereas the intramuscular group received an intramuscular injection of pethidine (0.5 mg/kg intragluteally in a solution of 15 ml and a simultaneous injection of 15 ml of normal saline infraspinally).

Figure 2: Box plots with visual analog scale pain scores after cough over the 24 h postoperative period after arrival in the gynecology ward. Data are presented as median visual analog scale with 25th to 75th percentiles (box) and range (whiskers).

Figure 3: Box plots with visual analog scale pain scores at rest over the 24 h postoperative period after arrival in the gynecology ward. Data are presented as median visual analog scale with 25th to 75th percentiles (box) and range (whiskers).

Figure 4: Box plots with sedation scores (scale 0–10) over the 24 h postoperative period after arrival in the gynecology ward. Data are presented as median sedation scores with 25th to 75th percentiles (box) and range (whiskers). *P < 0.05

Pethidine as a local analgesic agent

Pethidine is a weak opioid that exerts its analgesic effect by blocking voltage-dependent sodium channels on the nerve endings and also by interacting with μ- and δ-opioid receptors. Furthermore, Oztürk et al. showed that perineural administration of pethidine blocked both sensory and motor conduction in a dose-dependent way, thus when pethidine concentration was reduced from 2% to 1%, the degree of regional block achieved was reduced considerably.

The outcomes of this study are not in consequence with previous research on the local analgesic efficacy of pethidine. It has been analyzed that reduced pain scores could be attributed to its analgesic effects, mostly by systemic absorption and interaction with peripheral opioid receptors, whereas the duration of its analgesic effect up to 24 h could only be explained due to its local anesthetic properties. Moreover, there are several studies evaluating the local analgesic efficacy of pethidine, especially in achieving peripheral blocks. Onutu et al. showed that WI analgesia using pethidine exerts a postoperative analgesic effect in patients undergoing total hip arthroplasty, mostly by blocking voltage-dependent sodium channels.
so we hypothesized that it was unlikely that the WI group had received different surgical infiltration approaches since the analgesic solution was injected in the peritoneal layers following the same pattern.

There might be other concerns regarding the “optimal” dose of pethidine that we decided to deliver to each group. Previous studies examining the efficacy of pethidine as a local anesthetic solution infiltrated postoperatively into the surgical wound, commonly use a solution of 1%, even in surgeries where the incision is much smaller and more superficial than those concerning the abdominal cavity. For example, WI with 1% pethidine after uncremented total hip arthroplasty revealed an opioid-sparing effect for the first 24 postoperative h, whereas other studies showed that when the concentration of pethidine is reduced from 2% to 1%, the efficacy of the block declines.[23]

As far as sedation score is concerned, we decided not to evaluate the sedation effect of opioids according to the validated Ramsay Sedation Scale, although it is a more established method. This had to with the fact that it was more convenient for our patients, in the postoperative period with residual anaesthesia, to respond to this 0–10 numeric scale.

Finally, our observations were limited to the first 24 h of the postoperative period. Thus, we did not examine the implications of our analgesic interventions on our patients as far as early ambulation and discharge from the hospital are concerned or even the development of chronic neuropathic pain.

**Conclusions**

Our study with the intrafascial WI of 0.5 mg/kg pethidine, as a part of a multimodal analgesia regimen in patients undergoing TAH under general anesthesia, showed that morphine consumption was consistently, but not significantly, lower in the IM group as compared to the WI group, at all examined time points. In a matter of clinical importance, the results of our study were not in accordance with previous studies. Further investigation may be required to examine whether a higher dose of pethidine must be employed to exert its local anesthetic properties.

**Acknowledgments**

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**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

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