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Pethidine's Half-life Alterations following Orthopedic Surgery: Is Available Literature Always Compatible with the Data Obtained at the Bedside?

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ABSTRACT

Background: It is suggested that surgery results in changes in kinetic profile of some medication. The aim of this study was to investigate possible alterations in pethidine's half-life in postoperative pain management following orthopedic surgery of the inferior limb.

Methods: Twelve patients, who were classified as class I patients according to the American society of anesthesiologists physical status classification, were enrolled. Following the surgery of the lower limb, 25 mg of pethidine was injected intravenously. After that, 5, 30, 60 and 180 minutes following the injection, blood samples were taken and concentration of pethidine in blood samples was measured by High Performance Liquid Chromatography method. Moreover, patients' pain levels were assessed on visual analogue scales.

Results: The average half-life of pethidine was measured to be 29.68 minutes. Thirty minutes after the injection, significant relationship between plasma levels of pethidine and pain scale was reported (p= 0.041, r= 0.595). Moreover, men were found to perceive more pain than women. Pain scale was considerably different between smokers and non-smokers (p= 0.006), although blood concentration of pethidine was not significantly different between these two groups (p=0.09).

Conclusion: The average half-life of pethidine was shorter compared to the established half-life in literature. Orthopedic surgery most probably results in alterations in pharmacokinetic profile of pethidine. Moreover, gender and smoking status of the patients influence pain perception. Thus, pharmacokinetic alterations due to inferior limb orthopedic surgery, gender-related factors and smoking status of the patients should be considered in pain management in clinical settings.

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Introduction

Post-operative pain management is one of the key components of effective post-surgical patient care which aims at ensuring acceptable individual pain levels to facilitate rehabilitation and reduce morbidity and hospitalization (1). Indeed, acute pain after surgery may lead to changes in the responsiveness of the nociceptive system which includes both peripheral and central sensitization. Consequently, the transition from acute to chronic pain may occur (2).

Although post-operative pain management has gained significant attention during the last decades, it still remains to be a challenge for anesthesiologists and post-operative pain continues to be undertreated (3). Moreover, it is reported to be poorly addressed in many countries and approximately 80% of world's population is estimated to be inadequately treated for moderate to severe pain (4). Post-operative pain management has been traditionally provided by administration of opioids and there is evidence that systemic opioid administration is the most effective option in providing pain relief following major surgical procedures (5).

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However, excessive opioid usage is associated with a variety of side effects which prevents administration of adequate doses of opioids (6). Moreover, pain intensity is an important variable which guides treatment decisions (7).

Pethidine is known to be a commonly-prescribed postoperative opioid analgesic (8). It has been suggested that surgery may affect pharmacokinetics of some medication. There have been few studies on the effects that surgical procedures may exhibit on pharmacokinetics of medication used for postoperative pain management. According to our knowledge, to date, no one has studied the effects that orthopedic surgery of lower limbs may exhibit on pharmacokinetics of pethidine. Thus, this study was conducted with the hope of shedding light on possible pharmacokinetic alterations of pain medication following surgical procedures. The primary objective of this study was to investigate possible relationship between blood levels of pethidine and intensity of pain in patients following orthopedic surgery of the inferior limb. Secondary objectives included evaluation of possible relationships between gender and pain perception as well as between smoking status of the patients and pain perception.

Methods

The present prospective observational study was conducted at "Sina" Hospital, Tehran, Iran during November 2015 and April 2016. Twelve patients who underwent orthopedic surgery of the lower limbs and were classified as class I patients (according to the American society of anesthesiologists physical status classification) were included in this study. They were all between the age range of 18 and 35 years, had full consciousness and were experiencing post-operative pain. Exclusion criteria included pregnancy, lactation, having seizures, having history of drug abuse, suffering from major illness (e.g. cardiovascular disease, acute renal or liver disease, cancer or active malignancy), having psychiatric disorders, undergoing emergency surgical operations and having abnormal paraclinical tests. This study was approved by ethics committee of Tehran Medical Sciences, Islamic Azad University (No: IR.IAU.PS.REC.1394.5) and all the patients were informed of the study procedure and signed written consent forms. Moreover, the study was registered in Clinical Trials Registry (Registration No: IRCT201508093106N28). Sample size selection was done according to the previous pharmacokinetic study of pethidine in intraabdominal surgery (9).

After the surgery, following transfer of the patients to the recovery section, 25 mg pethidine was injected intravenously using standard method for spinal anesthesia for pain control. Then, 5, 30, 60 and 180 minutes after injections, blood samples were taken and concentrations of pethidine in blood samples were measured by High Performance Liquid Chromatography (HPLC) method. Moreover, patients' pain intensity was assessed on visual analogue scale (VAS). The instrument consisted of 10 scale items reporting pain intensity of the participants ranging from 0 (I have no pain) to 10 (I have maximum level of pain) and was used as indicator of the subjective pain. Validity and reliability of VAS was tested in previous studies (10). Patients were visited by an anesthesiology resident prior to the surgery who described VAS for them.

The primary endpoint was assessment of possible relationship between pharmacokinetic alterations of pethidine and intensity of pain in patients undergoing lower-limb surgery. As secondary outcome measures, possible relationships between gender and pain perception of the patients as well as between smoking status of the patients and pain perception were investigated. Moreover, any possible adverse drug reactions were monitored. Obtained data were analyzed by SPSS 18.0 software. Paired sample T-tests and independent sample T-tests were used to evaluate possible differences in blood concentrations of pethidine and pain intensity. P-values less than 0.05 were assumed significant.

Results

Twelve patients initially were included in this study. Six patients (50%) were male and six (50%) were females.. Mean age of the patients was 30.25 years. Moreover, mean ages of female and male patients were reported to be 31.0 and 29.5 respectively. Thus, age differences between male and female patients were not significant (P> 0.01). Demographics of the patients are shown in Table 1.

Table 1. Demographics of the Patients.

Variables	No. (%) of Participants[a]
Gender	
Female	6 (%50)
Male	6 (%50)
Age	
18-22	1 (%8)
22-26	2 (%17)
26-30	3 (%25)
30-34	6 (%50)
Smoking	
Smokers	4 (%33)
Non-Smokers	8 (%66)
Education	
Below Diploma	1 (%8)
Diploma	6 (%50)
Advance Diploma	3 (%25)
Master of Sciences/ Master of Arts	2 (%17)

a n=12

Five minutes following pethidine's injection, 9% of the patients experienced severe pain and 58% were reported to have moderate levels of pain. Moreover, 30 and 60 minutes following pethidine's injection, 58% of the patients

experienced moderate and 42% experienced minor pain. Additionally, 75% of the patients experienced moderate pain 180 minutes following pethidine's injection.

The average half-life of pethidine was measured to be 29.68 minutes. The average volume of distribution was calculated to be 3.49 L/kg.

Thirty minutes after pethidine's injection, a significant relationship was found between pethidine's concentration and pain scale (P= 0.041, r= 0.595). However, 5, 60 and 180 minutes following pethidine's injection, no statistically significant relationship was found between pethidine plasma levels and pain perception of patients (P< 0.05) (Table 2).

Table 2. Relationship between Pethidine Plasma Levels and Pain Perception.

Study	Correlation	p-Value
Plasma Level & Pain Perception 5 Min after Pethidine's Inj.	0.508	0.92
Plasma Level & Pain Perception 30 Min after Pethidine's Inj.	0.595	0.041
Plasma Level & Pain Perception 60 Min after Pethidine's Inj.	-0.386	0.216
Plasma Level & Pain Perception 180 Min after Pethidine's Inj.	0.096	0.766

Min= Minutes; Inj= Injection.

Pain perception was found to have significant differences between men and women (P=0.002). Men were found to experience more pain compared to women.

Intensity of perceived pain was considerably different between smokers and non-smokers (P= 0.006); however, blood concentrations of pethidine was not significantly different between smokers and non-smokers (P= 0.09). No significant side effects were observed

Discussion

Provision of adequate postoperative pain management is necessary to avoid development of peripheral and central sensitization which results from alterations in the nociceptive system following tissue damage during surgical procedures. Systemic opioid administration is known to be gold standard for reduction of moderate to severe acute pain after surgery (11). Importance of clinical pharmacokinetics measurements in pharmacotherapy of patients with intractable pain has been well established (12). Interindividual variations in pharmacokinetics of intravenous pethidine have also been manifested in a number of studies (13, 14). Moreover, surgery influences pharmacokinetics of drugs which can lead to subtherapeutic drug levels and consequently inadequate pain management (15, 16). According to this study, average half-life of pethidine was calculated to be 29.6882 minutes which is different from the reported half-life of pethidine in literature (2.5-4 hours). Thirty minutes after pethidine's injection, a significant relationship between pethidine's concentration and pain intensity was reported; however, no statistically significant relationship was found between plasma levels of pethidine and pain perception after 5, 60 and 180 minutes of pethidine's injection in patients undergoing orthopedic surgery of the lower limb. According to our knowledge, to date, no study has been conducted on possible effects of orthopedic surgery of lower limbs on pharmacokinetics of pethidine.

Gourlay et al., studied inter-and intra-individual alterations alterations in fentanyl plasma concentrations and pain perceptions of patients undergoing abdominal surgical procedures. Minimum effective concentration values remained constant in all patients over 48 hour's post-surgery (17). Moreover, Buhari et al., investigated the influence of surgery on the pharmacokinetics of tramadol in dogs. Consistent with the results of the present study, surgery exhibited significant effect on pharmacokinetics of tramadol (15). In another study, Waterman et al. compared pharmacokinetics of intramuscularly administered pethidine in healthy fully-conscious dogs and in the same dogs following anaesthesia and surgery. Similar with the results of the present study, plasma concentrations and analgesic properties of pethidine showed to alter following anaesthesia and surgery (18). Similarly, plasma concentrations of pethidine and its volume of distribution changed after anaesthesia and surgery in horses (19). Additionally, pharmacokinetics of pethidine was investigated during anaesthesia and patient-controlled analgesic therapy following major intraabdominal surgery. According to the results, pethidine should be prescribed by individualized regimens in surgical patients due to its altered pharmacokinetics during surgery and post-operative hours (9).

According to this study, pain perception was found to have significant differences between men and women. Indeed, men were found to experience more intense pain than women following orthopedic surgery. Research in the area of sex-related differences in pain perception has yielded different results. For instance, Ruau et al., studied pain intensity reported in electronic medical records of 11,000 patients and found significant differences in disease-specific pain in male and female patients. The most significant gender specificity in pain perception was found in patients with musculoskeletal, circulatory, respiratory and digestive system disorder (20). Moreover, clinical pain was reported with more severity and frequency and longer duration in women compared to men (21). Moreover, analgesic response has been found to differ between men and women. However, research in this arena has yielded conflicting results. Consistent with the results of this study, opioids were reported to produce greater analgesic responses in women than men (22). However, according to Aubrun et al., who studied sex-associated differences in pain perception and opioid requirements in a prospective

large-sample study, women experienced more severe postoperative pain compared to men and required a greater dose of morphine for postoperative pain management (23). Type of surgical procedure may indeed have an effect on pain perception of patients which was not taken into account in Aubrun et al., study. According to a recent metaanalysis which studied gender-related differences in postoperative pain perception in patients undergoing various surgical procedures, women were reported to have higher postoperative pain scores following thoracic, cardiac and neurosurgical procedures. However, studies investigating gender-associated differences in pain perception following abdominal and orthopedic surgeries yielded inconsistent results and larger prospective studies were suggested (24).

According to this study, pain perception had significant differences between smokers and non-smokers. These findings are in line with previous evidence that pain perception is reduced in smokers in comparison with non-smokers (25, 26). Indeed, nicotine is found to have analgesic properties (27). Moreover, administration of nicotine nasal sprays or transdermal patches is reported to reduce pain sensitivity in both smokers and non-smokers (26). According to a recent meta-analysis, perioperative nicotine administration was associated with significant reduction in postoperative opioid requirements. However, perioperative nicotine administration was associated with significant increased incidence of postoperative nausea in patients undergoing surgery with administration of general anaesthesia (28).

Anti-nociceptive and analgesic effects of opioids are observed after entrance to blood brain barrier and the effects do not necessarily have a strong relationship with plasma concentrations. However, measurement of CNS levels is quite complicated and after all, there is a correlation between brain levels and plasma concentrations (29).

In conclusion, according to the results of this study, alterations in plasma concentrations of IV-administered pethidine is observed following orthopedic surgery of the lower limbs which can be associated with inadequate pain relief and possible side effects. The average half-life of pethidine was reported to be different from the established half-life in literature. Thus, pharmacokinetics alterations due to inferior limb orthopedic surgery should be taken into account when pethidine is used as postoperative pain management. Moreover, gender and smoking status of the patients were found to influence pain perception. Therefore, gender-related factors and smoking status of the patients should be considered in pain management in clinical settings. In other words, unique pain management requirements for each individual should be defined.

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