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Small-Dose Fentanyl in Intravenous Versus Epidural Preemptive Analgesia

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Abstract: In this randomized, double-blinded study, the preemptive effects of intravenous and epidural fentanyl analgesia were compared with post-incisional analgesia in 40 patients undergoing orthophedic surgery of the lower extremities.

Patients were randomly allocated to one of two groups; intravenous or epidural analgesia, with twenty patients in each group. General anesthesia was induced with thiopentone 5-6 $mgkg^{-1}$ and maintained with 0.8-1.0% isoflurane and 66% nitrous oxide in 33% O_2. The trachea was intubated after administration of vecuronium 0.1 $mgkg^{-1}$. Patients in the epidural analgesia groups then received, by random allocation, 2 μgkg^{-1} fentanyl with 0.9% saline (total volume 0.15 $mlkg^{-1}$) after epidural catheter replacement 15 minutes before (preemptive epidural analgesia group-PEEA) or 15 minutes after (epidural analgesia group-EA) the surgical incision. Patients in the analgesia groups received, by random allocation, 2 μgkg^{-1} fentanyl intravenously immediately after induction (preemptive intravenous analgesia group-PEIV) or 15 minutes after the surgical incision (intravenous analgesia group-IV). Visual analogue pain scores (VAS) and postoperative morphine consumption in the preemptive groups were consistently lower than in the analgesia groups, although there was no statistical significance. Similarly, the first analgesic requirement time was longer in the PEEA group than in the EA group. Differences in the plasma concentration of glucose and cortisol were neither consistently nor significantly different between the study groups. In regard to these findings, we believe that with the management of patients with 2 μgkg^{-1} fentanyl intravenously or epidurally before painful stimuli lowers the VAS and postoperative analgesic use. Higher doses of fentanyl may be necessary for optimal and significant results.

Key Words: Analgesia, preemptive. Analgesics, opioid, fentanyl. Surgery, orthopedic.

Introduction

Surgical trauma induces nociceptive sensitization leading to amplification and prolongation of postoperative pain (1, 2). In experimental studies, acute pain behaviour or hyperexcitability of dorsal horn neurones can be prevented or preempted by administration of analgesic agents prior to injury (2, 3). However, the results of clinical studies have been less clear. NSAI agents, local anesthetics and opiods have been used for preemptive analgesia (4-10). Opioids offer potent analgesia especially in major surgical interventions associated with severe post-operative pain. In relatively few studies, opioids have been used alone for preemptive analgesia, with conflicting results (7, 8, 11, 12). Fentanyl is a synthetic opioid agonist producing a relatively rapid onset of analgesia and a moderate duration (13).

The aim of this study was to determine if intravenous and epidural analgesia with fentanyl before surgical incision had a preemptive effect on postoperative pain intensity, morphine consumption and plasma cortisol and glucose levels as compared to post-incisional analgesia in patients undergoing orthophedic surgery of lower extremities.

Methods

With the written approval of the local Ethics Committee, 40 patients (ASA I-II) aged 18-70 years

scheduled for elective lower extremity bone surgery were recruited to the study after informed consent was obtained. Patients with known alcohol or drug abuse, history of liver and renal disease, coagulation abnormalities, hypovolemia and opioid allergy were excluded. Patients were familiarized with the visual analogue pain scale (VAS) and were inroduced to the patient-controlled analgesia (PCA) pump and carefully instructed on its use. All patients received diazepam 10 mg and famotidine 40 mg orally 90 min before the operation.

After the electrocardiographic monitorization, patients were randomly allocated to one of two groups, intravenous or epidural analgesia, with twenty patients for each group. The anesthetist, patient and the assesor were blind to the patient's group allocation. In the epidural analgesia groups, after the patients were placed in the lateral position by the hanging drop sign technique, epidural catheters (No:16) were inserted via the L3-4 interspace by Tuohy needle and advanced 3-4 cm cephalad and flushed with normal saline.

General anesthesia was induced with thiopentone 5-6 $mgkg^{-1}$ and maintained with 0.8-1.0% isoflurane and 66 % nitrous oxide in 33% O_2, titrated to hemodynamic response. The trachea was intubated after administration of vecuronium 0.1 $mgkg^{-1}$.

Epidural analgesia groups patients then received, by random allocation, either 2 μgkg^{-1} fentanyl in saline 0.9% (total volume 0.15 $mlkg^{-1}$) after the epidural catheter replacement (PEEA Group) or same solution 20 min after surgical incision (EA Group). In order to neutralize any placebo effect, 0.15 $mlkg^{-1}$ saline was given epidurally 20 minutes after and 15 minutes before surgical incision in the PEEA and EA groups respectively.

Patients in the intravenous analgesia groups patients received, by random allocation, 2 μgkg^{-1} fentanyl intravenously immediately after induction (PEIV Group) or the same dose of fentanyl 15 min after surgical incision (IV Group).

All patients received 2 μgkg^{-1} fentanyl either intravenously (PEIV and IV Group) or epidurally (PEEA and EA Group) if their blood pressure and heart rates were greater than 25% of the initial values. In all groups, fentanyl doses were stopped 30 min before the end of operation.

All patients were tracheally extubated in the operating room after antagonism of residual neuromuscular blockade with 2 mg neostigmine and 1 mg atropine. All patients were then transferred to the recovery room and were assessed immediately. When the patients first complained of pain, a loading dose of morphine 5 mg (PEIV and IV groups) or 2 mg (PEEA and EA groups) was administered via the PCA device (Abbott Pain Management Provider). The PCA pump was set to deliver a 1 mg intravenous (PEIV and IV Group) or 0.5 mg epidural (PEEA and EA Group) bolus dose of morphine with a lock-out time of 10 min (PEIV Group and B) and 20 min (PEEA Group and D), a maximum dose of 10 mg (PEIV and IV Group) or 3 mg (PEEA and EA Group) in any 4 h period, and 0.3 mgh^{-1} (PEIV and IV Group) or 0.2 mgh^{-1} (PEEA and EA Group) basal infusion. This regimen of PCA was continued on the ward for 48 h, during which time no other analgesic was administered.

Blood samples were obtained pre-operatively, as well as 15 minutes, 60 minutes, 4 h, 8 h, 24 h and 48 h after surgical incision. Plasma glucose concentration was measured by a Hitachi analyzer (glucose oxidize method) and plasma cortisol concentration by radioimmunoassay .

A 10 cm visual analogue scale (VAS) (with endpoints labeled "no pain" and "worst possible pain") was used to assess pain intensity 4 h, 6 h, 12h, 24 h, and 48 h after completion of surgery. Side effects (nausea, vomiting, pruritus, sedation, respiratory depression) were recorded if present, and requirements for other drugs were noted.

Data Analysis

Parametric data are presented as standard error of mean (SEM), and non-parametric data are presented as frequencies or percentages. Ordinal data were compared by the Kruskal-Wallis and Mann-Whitney –U tests. Friedman and Wilcoxon was used for ordinal data within the same group. Cateorical data were analyzed with the X^2 test. We considered $p<0.05$ to be significant.

Results

Table I shows demographic and clinical variables for groups. There were no significant differences between groups in age, weight, sex, time from induction of anesthesia to skin incision and length of operation ($p>0.05$).

Figure 1 shows the visual analogue scores for pain at rest 48 h postoperatively. There were no statistically significant differences between either the PEIV and IV groups, or the PEEA and EA groups, but the two epidural groups had significantly lower scores than the intravenous groups at 12, 24 and 48 h after the operation ($p<0.05$). VAS pain scores were lower in the PEIV group than in the IV group at all times ($p>0.05$). Similarly, VAS pain scores in the PEEA group were lower than in the EA group at 6, 24, and 48 h after surgery ($p>0.05$).

Table 1. Physical charactheristics, time from induction to incision and duration of operation in groups.

	PEIV Group	IV Group	PEEA Group	EA Group
Age (year)	47.50±6.76	34.20±3.71	48.43±4.36	52.00±3.83
Weight (kg)	70.10±3.28	69.40±4.03	73.00±3.92	76.33±1.83
Sex (M/F)	4/6	6/4	4/6	3/7
Time from induction to incision (min)	26.50±3.25	26.87±3.39	27.50±3.09	35.00±2.44
Length of operation (min)	140.00±22.09	123.50±11.11	130.00±19.94	128.89±14.78

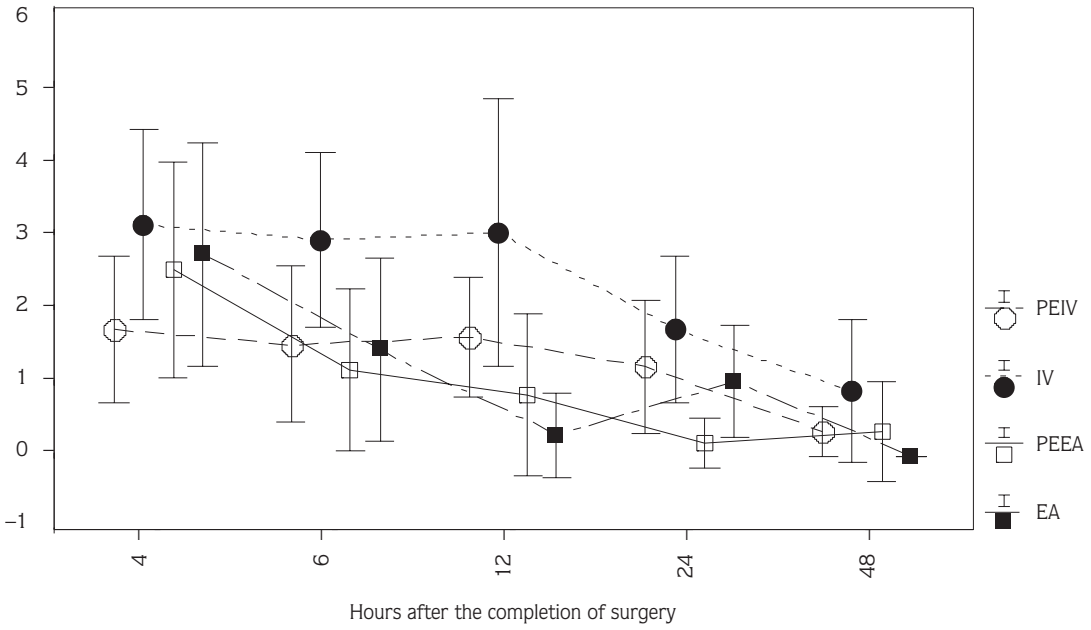

Figure 1. VAS in four groups over 48 hours postoperatively.

Table II shows total morphine consumption doses for 48 h after the operation, and the time to the first postoperative analgesic demand. There were no significant differences between the PEIV group and the IV group or the PEEA group and the EA group, but PCA total morphine doses were lower in the PEIV group than in the IV group and the PEEA group than in the EA group ($p>0.05$). Total morphine consumption doses were significantly higher in the intravenous groups than in the epidural groups ($p<0.01$). The time to the first postoperative analgesics demand was longer in the PEEA group than in the EA group ($p>0.05$). In addition, the time to the first postoperative analgesic demand of the epidural groups was longer than for the intravenous groups ($p<0.01$).

However, glucose levels were lower in the PEEA group than in the other groups at all times, although the difference was not statistically significant ($p>0.05$) (Figure 2). There were significant differences only at 60 minutes to baseline cortisol levels in the PEIV Group and EA Group ($p<0.01$, $p<0.05$, respectively) (Figure 2).

All patients remained cardiovascularly stable throughout the operation, although one patient in the PEIV group required fentanyl 125 µg during the operation.

Incidences of nausea and vomiting were higher in epidural groups (30%) than in the intravenous groups (15%). Six patients in the intravenous groups and one patient in the epidural groups had some degree of sedation, but no clinically significant respiratory depression occured in either group.

	PEIV Group	IV Group	PEEA Group	EA Group
PCA total morphine dose over 48 h (mg)	30.08±3.77	35.52±3.85	13.80±1.13	16.46±3.60
Time to the first postoperative analgesic demand (min)	18.70±2.60	19.60±2.61	36.71±5.26	30.56±3.17

Table 2. PCA total morphine consumption and time to the postoperative analgesic demand (mean ±SEM).

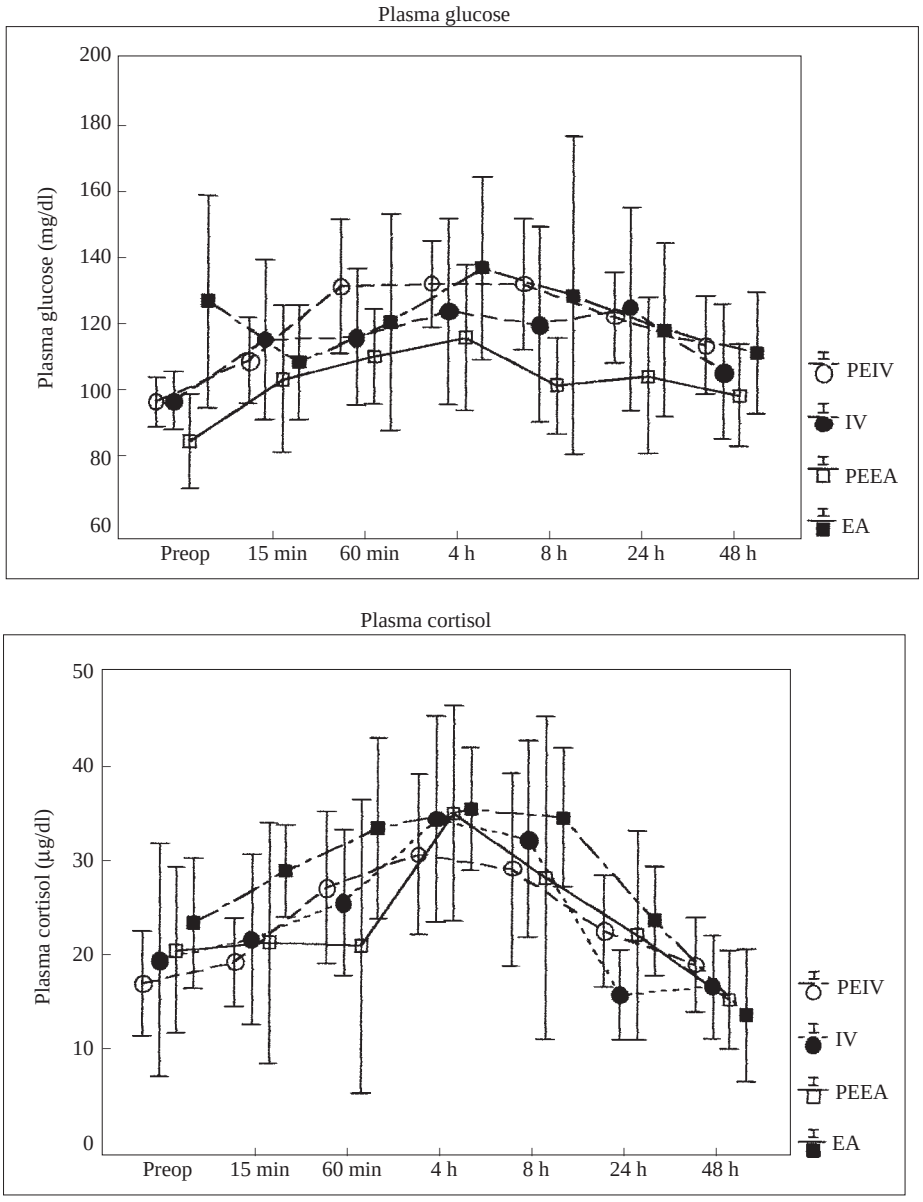

Figure 2. PCA total morphine consumption and time to the postoperative analgesic demand (mean ±SEM).

Discussion

Our results show consistently lower VAS pain scores and postoperative morphine consumption in the preemptive groups than in the analgesia groups, and suggest a preemptive effect, although no statistically significant differences could be shown. Similarly, the longer first analgesic requirement time in the PEEA group as compared to the EA group may also support preemptive analgesia. On the other hand, low serum cortisol levels at 60 min in the PEEA group may indicate that epidural preemptive fentanyl analgesia may be more effective in preventing surgical stress response than both epidural postincision and intravenous pre-postincision. In regard to these findings, we believe that with the management of the patient before the painful stimuli a preemptive effect can be achieved.

The statistically non-significant results are probably due to factors related to our study design. First of all, the low number of patients in our study groups may be insufficient to reveal statistical significances. Another factor may be the failure to achieve a blockade of afferent signals to the central nervous system. Insufficient afferent blockade may be due to insufficient fentanyl dose or incorrect drug application time. Fentanyl have been used in doses ranging from 1 μgkg^{-1} to 10 μgkg^{-1} for analgesic purposes (13, 14). Kiss and Killian showed that premedication with meperidine significantly decreased postoperative analgesic requirements (11). Campbell et al. administered 1 μgkg^{-1} fentanyl preoperatively for molar tooth surgery and reported no differences between treated and control groups (14). In contrary, Katz et al. found that patients given 4 μgkg^{-1} epidural fentanyl shortly before thoracotomy reported less pain and used less supplementary analgesic afterwards (15). On the other hand, in animal models it has been shown that much smaller doses of morphine prevent sensitization to pain and wind-up in the nervous system than are necessary to suppress it (16). As the information on the use of fentanyl in preemptive analgesia is very limited, we have used 2 μgkg^{-1} fentanyl, the routine analgesic dose in our clinic. It may be necessary to use higher fentanyl doses to achieve a statistically significant preemptive effect.

The timing of the drug injection in regard to skin incision is also important. With intravenous administration , the maximum effect is achieved within a few minutes. In epidural analgesia however, maximum analgesia is not obtained immediately and the timing of the drug administration in preemptive and non-preemptive groups is more critical. The onset of analgesia is more rapid with the highly lipid soluble opioids such as fentanyl and alfentanil, but, lipid insoluble opioids, such as morphine, are retained in the cerebrospinal fluid, providing a longer supply to the spinal cord and consequently a slower onset, but with a longer duration of analgesia after the administration of a single dose (17-19). The onset of analgesia after lumbar epidural fentanyl occurs as early as 4 minutes after injection, and peak analgesia occurs approximately 15-20 minutes later (19, 20). In our study, epidural fentanyl in the PEEA group was received at least 15 minutes before skin incision (30±3.45 min), as compared to 15 minutes after skin incision in the EA Group, so that noxious impulses would continue to reach the spinal cord for as long as thirty minutes after skin incision in the EA group, ensuring a definite difference in the central sensitization between the two groups.

Painful stimuli reaching the central nervous system produces a systemic neuroendocrine response called the stress response, and the prevention of the central sensitization is also expected to lower the related metabolic parameters. Under general anestesia, the lightly anesthetized spinal cord receives a massive afferent barrage produced by surgery, particularly when peripheral nerves are traumatized, and under regional anesthesia, the cord receives no afferent signals set off during surgery (1). Epidural opioids have the advantage of producing analgesia without motor or sympathetic blockade (17). Katz et al. explored the relationship between the surgical stress response and the development of postoperative pain in the context of pre-emptive analgesia and showed that pre-incisional local anesthetic blockade delayed neuroendocrine response to surgery but it did not attenuate the magnitude of the response (15). In this study, it was found that cortisol concentration was higher in preincisional group than in the postincisional group in only 30 min after incision (15). In a study using patient-controlled administration of fentanyl after cholecystectomy, no important effects were demonstrated on plasma catecholamine or glucose response while postoperative cortisol concentrations were moderately diminished, despite very good pain relief (21). Similarly, in our study, differences in the plasma concentrations of glucose and cortisole were neither consistently nor significantly different between the study groups. Kehlet pointed out that very large doses of systemic opioids are necessary if a pronounced decrease in the stress response is required (22). In addition, this study mentioned that, despite reasonably good post-operative pain relief, these techniques have no major effect on the surgical stress response, although

occasionally an inhibition in some of the stress parameters has been demonstrated. Studies by Kehlet's group have clearly demonstrated difficulties in providing complete blockade of noxious stimuli during surgery, indicated by an increase in plasma cortisol concentration and other metabolic responses (22). Kehlet's results show that only an extensive epidural blockade from T4 to S5 prevents the cortisol response to lower abdominal surgery. In an editorial comment, Kiss and Killian pointed out that whether antinociceptive treatment given before incision is more effective than that given afterwards, is an important question, but this should be distinguished from the question of whether perioperative antinociceptive treatment reduces subsequent postoperative pain (11). Since stress related metabolic changes are not exclusively related to noxious stimuli but, depending on the anatomical location, duration and extent of the surgical procedure, local tissue injury also contributes to changes in the plasma concentrations of the so-called stress factors, we believe that analysing the advantageous metabolic effects of the preemptive analgesia cannot be achieved without standard and sensitive methodology.

In conclusion, although we have failed to show statistically significant differences attributable to preemptive analgesia, our results suggest that preincisional administration of either intravenous or epidural 2 μgkg^{-1} fentanyl lowers the postoperative analgesic use and prolongs the first analgesic requirement time. Higher doses of fentanyl may be necessary, for optimal and significant results.

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