

Preoperative versus Postoperative Pethidine for Extraction of Impacted Third Molars

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Abstract

We have studied the pre-emptive analgesic effects of pethidine by comparing its analgesic effects given before or immediately after operation in a randomized, double-blind study of 40 patients undergoing removal of bilateral impacted third molars under general anaesthesia. Group 1 patients received pethidine 50 mg as a 1 ml injection 1 to 2 hours before operation and normal saline 1 ml intramuscularly immediately after surgery. Group 2 patients received normal saline 1 ml intramuscularly before operation and pethidine 50 mg as a 1 ml injection immediately after surgery.

Outcome measures included perception of pain on a visual analogue scale (VAS), the number of patients who required postoperative pethidine, time to first postoperative pethidine injection and total dose of pethidine given. Four patients in group 1 compared to 8 in group 2 required postoperative pethidine but this was not statistically significant. The VAS scores, time to first postoperative pethidine injection and total dose of pethidine also did not differ significantly between the 2 groups. We concluded that preoperative administration of pethidine intramuscularly did not confer additional analgesic effects compared with a similar dose given after surgery.

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Introduction

Experimental studies of nociception have shown that peripheral tissue injury provokes two kinds of modification in the responsiveness of the nervous system: peripheral sensitization, a reduction in the threshold of nociceptor afferent peripheral terminals, and central sensitization, an activity-dependent increase in the excitability of spinal neurons.^{1,2} The neurophysiological mechanisms may involve windup, that is amplification of noxious afferent input, lowering of thresholds for transmission of pain and after-discharge of dorsal horn neurons.³ Together, these changes contribute to the postinjury pain hypersensitivity state postoperatively, which manifests as allodynia (innocuous stimuli generating pain) and hyperalgesia (increased pain to sub-threshold stimulation).

Recent studies on nociception suggest that preoperative regional anaesthesia or opioid premedication can pre-empt postoperative pain by preventing the establishment of central sensitization. This leads to the con-

cept of pre-emptive analgesia, that is the attenuation of postoperative pain if the transmission of nociception is blocked before the occurrence of noxious stimuli.⁴

Pre-emptive treatment may be directed at the periphery, at inputs along sensory axons, and at central neurons by using opioids, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, either alone or in combination.⁵ Systemic opioids act both presynaptically to reduce neurotransmitter release and postsynaptically to hyperpolarize the membrane of dorsal horn neurons. Thus, these drugs would be expected to prevent buildup of primary afferent-evoked depolarization in dorsal horn neurons and hence, central sensitization.^{6,7}

Pethidine is a synthetic opioid agonist derived from phenylpiperidine which is formulated for subcutaneous, intramuscular and intravenous use as well as for central neuraxial blockade. It is an effective analgesic postoperatively.

This study was designed to compare the preoperative and postoperative analgesic effects of intramuscular

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pethidine in a randomized, double-blind study of patients undergoing extraction of bilateral impacted third molars.

Patients and Methods

After obtaining local Ethics Committee approval and informed consent, we studied 40 ASA I (American Society of Anesthesiologists) patients, that is healthy patients with no systemic illnesses undergoing removal of bilateral impacted third molars under general anaesthesia. Subjects were screened for inclusion in the study on the basis of having bilateral symmetrically positioned impacted third molars with equally anticipated degree of difficulty of extraction. Patients with known allergy to any opioids were excluded. Patients with any systemic illnesses were excluded as they may have altered pharmacokinetic handling of the drug which may influence the results.

Patients were allocated randomly to two groups: group 1 (mean age 21.3 years; mean weight 54.3 kg) received pethidine 50 mg intramuscularly 1 to 2 hours before surgery and normal saline 1 ml intramuscularly immediately after surgery; group 2 (mean age 22.8 years; mean weight 55.4 kg) received the same injections in reverse order.

No premedication was given. General anaesthesia was induced with intravenous propofol 1 to 2 mg/kg and intravenous fentanyl 1.5 µg/kg and maintained with isoflurane 0.5% and 70% nitrous oxide in oxygen. Atracurium 0.3 to 0.5 mg/kg was used to facilitate tracheal intubation and maintain neuromuscular blockade. No local anaesthetic was given.

During the study, each patient received two identical, coded 1 ml injections; one containing pethidine 50 mg, the other containing normal saline. All the patients received the first injection 1 to 2 hours prior to surgery and the second at the conclusion of the surgery. The sequence of drug-placebo administration was then identified for each patient after the end of the study period.

Patients were asked to grade the intensity of postoperative pain on a 100 mm visual analogue scale at 30 minutes, and at 1, 3, 6 hours after surgery. These values were recorded by the nursing staff who were unaware of the sequence of administration of the injections. If analgesia was inadequate, as deemed by a visual analogue score of 50 mm and above, then pethidine 50 mg intramuscularly was administered accordingly.

The results were analysed by Mann-Whitney U test for non-parametric data, unpaired t-test for normally distributed data and chi-square analysis for categorical data. A postoperative reduction in visual analogue score of 2.0 cm was deemed clinically significant, and the mean was 2.0 cm. Hence, the power of the study to detect a true difference between the two groups was 80% for $P < 0.05\%$.

Results

Group 1 and group 2 patients were all healthy ASA I patients. There were no significant differences in terms of age, weight, sex or the duration of anaesthesia between the two groups (Table I).

Median pain scores on the visual analogue scale were similar at all times (Table II).

Patients requiring postoperative analgesia received pethidine 50 mg intramuscularly in accordance with the visual analogue score. Four patients in group 1 compared to 8 patients in group 2 received postoperative pethidine but this was not statistically significant. Patients in group 2 required more postoperative analgesia and the interval to the first dose was shorter but these results did not reach clinical significance (Table III)

TABLE I: DEMOGRAPHIC CHARACTERISTICS AND DURATION OF ANAESTHESIA BETWEEN THE 2 GROUPS.

	Group 1	Group 2	P
Age (mean) years	21.3 ± 3.4	22.8 ± 4.9	0.2
Weight (mean) kg	54.3 ± 9.1	55.4 ± 7.3	0.2
Sex (F:M)	10:10	10:10	0.0
Duration of anaesthesia (min)	82.5	84.0	0.9

TABLE II: VISUAL ANALOGUE SCALE PAIN SCORES (median - interquartile range)

	Group 1 median (range)	Group 2 median (range)	P
30 min	1.2 (0-3.9)	1.1 (0-4.8)	0.9
60 min	2.0 (0-5.2)	2.2 (0-5.2)	0.7
3 h	2.4 (0-3.6)	4.2 (1.8-6)	0.1
6 h	1.1 (0-3.3)	2.5 (1.5-4.8)	0.1

Statistical significance $P < 0.05$. Mann-Whitney U test.

TABLE III: POSTOPERATIVE PETHIDINE REQUIREMENTS (MEDIAN)

	Group 1 (n = 20)	Group 2 (n = 20)	P
Received pethidine (n)	4	8	0.1
Total dose (mg)	63.8	67.5	0.27
Interval to 1st dose (min)	279.4	231.6	0.74

Discussion

Experimental studies on nociception have suggested that tissue injury and trauma lead to postinjury neuroplasticity and "windup", which may lead to pain hypersensitivity.² Nociception has been unequivocally attenuated by pre-emptive analgesia, but similar human studies have yielded conflicting results.

The pre-emptive effects of NSAIDs have been studied in patients undergoing removal of impacted third molars. Naproxen given orally 30 minutes after surgery

provided an effective postoperative analgesia as an equal dose given orally 30 minutes before surgery.⁸ In a similar group of patients, the combination of flurbiprofen administered before and after surgery provided more effective postoperative analgesia than when flurbiprofen was given only after surgery.⁹ This is not unexpected as the total dose of NSAIDs was larger in the combined treatment group, and thus the results did not demonstrate the increased efficacy of pre-emptive analgesia compared with postoperative treatment.

In other studies the pre-emptive analgesic effects of opioids were reviewed. In a non-randomized, placebo-controlled double-blind study in patients undergoing transsternal thymectomy, preoperative extradural morphine 7 mg compared with saline had no effect on postoperative pain scores at rest or on additional analgesic requirements beyond the initial 8 hour postoperative period.¹⁰ However, the study was small with only 19 patients. In another randomized, placebo-controlled study, a preoperative bolus of alfentanil 30 µg/kg followed by an intraoperative infusion of 40 µg/kg/h had no effect on postoperative pain scores or requirement for additional opioids.¹¹ These two studies therefore do not demonstrate the efficacy of pre-emptive analgesia.^{10,11}

In a non-randomized study in patients undergoing lumbar disc prolapse surgery and receiving a variety of premedicant drugs, Kiss and Kilian¹² concluded that additional opioid premedication reduced time to first demand for a postoperative analgesic and the overall need for postoperative analgesia. However, due to major methodological deficiencies, and differences in the sex distribution, that study was unable to demonstrate conclusively that opiate premedication diminishes the sustained hyperexcitability of the central nervous system caused by intraoperative stimuli.¹²

The outcome for our randomized, double-blind study demonstrated that there was no significant effect of the timing of pethidine administration in the need for postoperative analgesia between the two groups. The group that received preoperative pethidine did not require as much postoperative analgesia as the group that did not receive preoperative pethidine. Although VAS scores were generally higher in the group that did not receive preoperative pethidine, this did not reach statistical significance. Similarly, the overall pethidine requirements were higher and the time to pethidine requirements postoperatively shorter in the group that did not receive preoperative pethidine; however, a statistical significance could not be demonstrated. Nevertheless, the outcome measure nearest to significance [number of patients requiring postoperative pethidine ($P = 0.1$, Table III)] was weakly suggestive of pre-emptive analgesia. The power of this study to detect a difference was 80% and to obtain a power close to 100% may be

extremely difficult in a purely clinical situation. It is possible that with a larger sample, a statistical significance may be demonstrated.

The difference between the highly significant results of pre-emptive analgesia in experimental models and clinical studies may have several explanations. Although central sensitization may contribute to postoperative pain in humans, surgical trauma differs from the conditioned stimuli applied in most experimental studies. Contrary to a well-localized thermal or chemical injury, or brief C-afferent stimulation, the afferent input to the central nervous system during and after surgery is prolonged and extensive, with mixed cutaneous, muscular and visceral components. Central sensitization may be generated not only during surgery, but also postoperatively due to persistent inflammation and hyperalgesia at the wound site. Thus intraoperative nociceptive block may not be adequate to reduce postoperative sensitization of central neurons.¹³⁻¹⁵

In experimental settings, preinjury opioids have been shown to prevent central sensitisation.¹⁶ This finding has yet to be borne out in clinical situations. If this can be confirmed clinically, the question of the optimal drug, route, dose, and timing of opioids to prevent postoperative pain needs further investigation. Preoperative injections are painful and may lead to nausea and sedation and the question would then need to be raised whether intravenous opioids administered immediately after induction but before surgical stimulation will be as effective as intramuscular injections given an hour or so before surgery.

In conclusion, surgical stimulation can outlast the relatively short-lived effect of a single pre-emptive analgesic, with the result that central sensitisation may occur even after surgery, when preoperative nociceptive block has terminated. A multi-modal or "balanced analgesia" approach, including pre-emptive analgesia with an opioid and application of local nerve blocks and steroids may provide better analgesia in this group of patients.

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