

Intravenous indomethacin for postoperative pain

A double-blind study of ankle surgery

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Intravenous indomethacin infusion (75 mg/10 h) for relief of pain after ankle surgery was compared with placebo in a double-blind study. Ninety-seven patients were operated on for a malleolar fracture or ruptured ligament of the ankle under single-dose spinal anesthesia. In the indomethacin group, 14 out of 49 patients were free from pain, 4/47 in the control group. Severe pain was experienced by 24/49 in the indomethacin group and by 41/47 in the control group. Supplementary intramuscular oxycodone was needed for 24 patients in the indomethacin group and for 41 control patients. In 1 patient, i.v. indomethacin administration caused serious arterial hypotension necessitating discontinuation of the medication.

Intravenous indomethacin reduced the need of opiate for alleviation of postoperative pain, but the possibility of hypersensitivity reaction calls for particular attention.

Tissue damage causes increased prostaglandin synthesis and release of different neuronal pain transmitters. Anti-inflammatory analgesics, which inhibit prostaglandin synthesis, have proved to be effective alone (Lindgren and Djupsjö 1985) or in combination with opiates (Reasbeck et al. 1982, Cashman et al. 1985, Jones et al. 1985).

We report a double-blind comparison of the effect of continuous intravenous indomethacin compared with a placebo in relation to the need of intramuscular opiate.

Patients and methods

The series included 97 patients who gave informed consent. Exclusion criteria were allergy to anti-inflammatory analgesics, asthma, increased bleeding tendency, heparin prophylaxis, pregnancy, and age under 16 years.

The patients were operated on because of

malleolar fracture or ligament rupture of the ankle. One hour prior to operation, the patients received 10 mg diazepam by mouth. For spinal anesthesia, 3 ml = 15 mg isobaric 0.5 per cent bupivacaine (Marcain® 0.5%, Astra AB, Sweden) was used. The subarachnoid space was punctured between the 2nd and 3rd lumbar vertebrae. The subarachnoid block was successful in all the cases, and no patient required any supplementation with analgesics during the operation. The duration of the operations was 20-40 min.

The patients were randomly allocated to one treatment and one control group. At the end of the operation, the indomethacin group received 25 mg indomethacin (Confortid®, A/S Dumex, Copenhagen) mixed in 100 ml of saline and given as intravenous infusion for 10 min followed by an infusion of 1,000 ml isotonic saline containing 50 mg indomethacin. This infusion was given over a period of 10 h at a rate of 5 mg indomethacin per hour. In the control group, the patients received 1,000 ml of saline at a similar infusion rate. The trial was double-blind with coded numbers for the nursing staff in the recovery room and at the surgical ward.

In the indomethacin group, there were 49 patients of 42 ± 13 years of age weighing 75 ± 13 kg.

Corresponding figures in the control group were 47, 44 ± 14 years and 76 ± 16 kg. There were 21 females and 28 males in the indomethacin group and respectively 22 and 25 in the control group.

Pain, consciousness, and side-effects were recorded on a special form by nurses. The intensity of pain was reported by the patient to the same nurse every hour or more often, recorded as no, moderate, or severe. The observation period covered 12 hours. When the patients complained of pain and asked for analgesic, they received 0.14 mg/kg oxycodone intramuscularly. The number of doses and the times of injections were recorded.

The Students *t*-test and chi-square analysis were used.

Results

Nausea and vomiting occurred in 3 patients in the indomethacin group and in 9 patients' in the control group. One patient, who was allocated to receive indomethacin, had serious hypotension at infusion. Hence, it was immediately stopped and the blood pressure normalized without any special treatment. When the drug infusion was resumed after approximately 15 minutes, the systolic blood pressure decreased to 60 mmHg. After discontinuation of the drug infusion and accelerated infusion of saline, the blood pressure returned to normal within a few minutes. There were no other symptoms of allergic reaction. After these short episodes of hypotension, the patient recovered completely. She was excluded from the study.

The control patients experienced more pain and requested more oxycodone than those in the indomethacin group (Table 1). There were 14

treatment patients out of 49 who did not complain of pain at all, compared with 4 control patients out of 47, and 24 indomethacin patients and 41 control patients complained of severe pain ($P < 0.001$).

Discussion

Reasbeck et al. (1982) reported a reduction in the request of opiates by patients postoperatively receiving a daily prophylactic dosage of 300 mg of indomethacin as suppositories. However, indomethacin cannot be expected to replace the need for opiates, but to maintain a better continuous analgesia, as shown also by Jones et al. (1985). According to Tigerstedt et al. (1981), mild analgesics such as lysine acetyl salicylate can replace up to roughly 5 mg oxycodone per dose.

The dose of indomethacin in our study was relatively low. In urethral colics a single intravenous dose of 50 mg is recommended and a maintenance dose of 7.5 mg/h is often routinely used postoperatively without untoward effects.

In this study, intravenous indomethacin was given prophylactically by continuous infusion. The aim was to prevent the increase of prostaglandin synthesis at the site of surgical trauma. Indomethacin, as other anti-inflammatory analgesics, has no effect on activated prostaglandins. This can be the explanation of negative results in studies where the anti-inflammatory agent was not given until the patient complained of pain (Dundee and McAteer 1981, Editorial 1980).

Nausea and vomiting are well-known side-effects of opiates, and thus reduction of the need for opiates should reduce these symptoms. This was clearly demonstrated by Mattila et al. (1983), Cashman et al. (1985) and Lindgren and Djupsjö (1985), but was only seen in our study as a trend.

Hypersensitivity and bronchial asthma must be considered when using anti-inflammatory analgesics. Leucotriens can cause bronchoconstriction or vasodilatation and increased permeability of capillaries. This mechanism can evoke untoward clinical symptoms in patients with inherent sensitivity. One of our patients had a sudden hypotensive episode. The incidence of this type of serious reaction cannot, however, be determined from 1 case in a series of 49 patients, as few reactions of this type have been reported in relation to the large amount of indomethacin used in different application forms.

Table 1. Evaluation of pain after ankle operations

Degree of pain	Indomethacin n 49	Placebo n 47	Significance
None			
Malleolar	10	2	
Ligament	4	2	
Total	14	4	$P < 0.001$
Moderate			
Malleolar	10	1	
Ligament	1	1	
Total	11	2	$P < 0.001$
Severe			
Malleolar	20	33	
Ligament	4	8	
Total	24	41	$P < 0.001$

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