COMBINED TREATMENT WITH INDOMETHACIN AND LOW-DOSE HEPARIN AFTER TOTAL HIP REPLACEMENT

A DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL

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We studied the safety of combining the postoperative use of a non-steroidal anti-inflammatory drug with low-dose heparin. In a double-blind, placebo-controlled clinical trial we reviewed the complications in 235 patients after total hip replacement, all treated with low-dose heparin and either indomethacin or a placebo.

The incidence and type of complications in the two groups were nearly equal; indomethacin-treated patients had no increase in complications related to bleeding. Postoperative bleeding into drains was marginally greater in the indomethacin group, although the difference was not statistically significant.

We conclude that treatment with indomethacin and low-dose heparin after hip replacement does not significantly increase the bleeding or other complications. We also found that patients receiving indomethacin were mobilised an average of one day before those on placebo.

There has been considerable interest in the use of non-steroidal anti-inflammatory drugs (NSAIDs) in the perioperative phase of major surgery. These drugs can provide adjunctive analgesic and anti-inflammatory effects, with positive action on the surgical stress response, and reduction of postoperative morbidity (Reasbeck, Rice and Reasbeck 1982; Keenan et al 1983; Thind and Sigsgaard 1988). Indomethacin has also been shown to reduce heterotopic bone formation after total hip replacement (Schmidt et al 1988) and, as a prostaglandin antagonist, to inhibit platelet adhesion (Helleberg 1981; Metz 1981).

Postoperative regimes after major operations often include low-dose heparin as prophylaxis against thromboembolic complications, and this is usually continued until the patient is mobile (Wessler and Gitel 1979). There has, therefore, been concern that the combined use of NSAIDs and anticoagulants might increase the risk of some complications, especially serious bleeding episodes or cerebrovascular accidents (Müller and Herrmann 1966; Odegaard 1974; Reasbeck et al 1982).

The present study reports the complications in a group of patients who were treated after total hip replacement with low-dose heparin in combination with either indomethacin or a placebo.

PATIENTS AND METHODS

From 1984 to 1986, at Kolding Hospital 342 total hip replacements were performed, and all the patients were evaluated for participation in a randomised, double-blind, placebo-controlled clinical trial of indomethacin in prevention of heterotopic bone formation. Of these, 89 were excluded because of refusal to participate or because of contra-indications to the use of indomethacin, leaving 253 patients for randomisation.

Treatment was started on the first morning after operation, with either indomethacin 25 mg or a placebo, given three times daily for six weeks. The marked influence of indomethacin in reducing the development of heterotopic bone has been reported elsewhere (Schmidt et al 1988). Prophylactic treatment with low-dose heparin...
combined with dihydrotgot-ergotamine (DHE) was given subcutaneously as 5000 IU twice daily, starting on the morning of surgery and continued until the patient was mobile.

Seven patients had prophylaxis with warfarin, either because of contra-indications to the use of DHE-heparin or because the patient had previously had this treatment for earlier thrombo-embolic complications. These patients were excluded from the study since there were too few to allow any conclusions to be made. Another 11 patients refused to participate in the study. Of the remaining 235 patients, 116 were randomised to the indomethacin group, and 119 to the placebo group.

All the arthroplasties were performed using a posterolateral approach. The joint capsule was excised and a cemented Lubinus total hip prosthesis was implanted. Prophylactic cephalosporin and gentamicin-impregnated bone cement were used in all patients. Postoperative drainage from subcutaneous and subfascial suction drains was measured. All patients had follow-up examinations at six, 12 and 52 weeks after arthroplasty.

The Mann-Whitney rank sum test was used for statistical analysis, only results with p values below 0.05 being considered significant. The trial was approved by the local ethical committee, and informed consent was obtained from all patients.

RESULTS
A total of 31 patients were secondarily excluded (Table I). The incidence of dyspepsia was approximately equal in the two groups, and no patient had gastric bleeding. In the indomethacin group one patient died two weeks postoperatively following an acute myocardial infarction and one died after a cerebral haemorrhage on the first postoperative morning. She had been randomised to indomethacin, but had not been given her first dose. Two patients complained of dizziness or slight confusion, two in the indomethacin group and one on the placebo, but these complaints settled after the trial medication was stopped.

In all, 204 patients completed the trial; their side effects and complications, evaluated after one year, are listed in Table II. The overall rate of complications was low and approximately equally distributed in the two groups. Six patients died during the first year. Of the two in the indomethacin group, one died after an automobile accident and one from a cerebral haemorrhage, but both several months after surgery. Four patients in the placebo group died, three from cancer and one following a myocardial infarct nine months after surgery.

Two patients, one in each group, showed signs of deep venous thrombosis but none developed signs of pulmonary embolism. Five patients had a wound haematoma, but only one of these had had indomethacin. One patient had a deep wound infection.

The indomethacin group had higher median post-operative bleeding (Table III), but the difference between the two groups was not statistically significant (p = 0.15). Table IV shows that the duration of postoperative prophylaxis with DHE-heparin was lower in the indomethacin group. The difference between the medians was highly significant (p = 0.0004).

DISCUSSION
The mechanism by which indomethacin influences the coagulation system is unclear, but it has been shown that indomethacin is a competitive inhibitor of cyclo-oxygenase, an important enzyme in the transformation of arachidonic acid into the prostaglandins. Two of these arachidonic acid metabolites, prostacyclin and tromboxane A-2, have been shown to take part in the modulation of haemostatic and thrombotic events (Harlan and Harker 1981). Clinical reports are conflicting. Some have concluded that indomethacin has little or no influence on the coagulation system (Müller and Herrmann 1966; Müller and Zollinger 1966; Wessler and Gitel 1979; Pullar and Capell 1982), but others, describing series in which indomethacin was given in addition to warfarin anticoagulation, showed that it did influence the coagulation system and enhance the risk of bleeding (Odegaard 1974; Baele, Rasquin and Barbier 1983). Baele et al (1983) studied oxametacin, an indomethacin equivalent, in patients who had been treated with warfarin for several months; they found a significant increase in the prothrombin time and the warfarin had to be temporarily stopped in four patients because of bleeding episodes. This observation has been confirmed by Odegaard (1974).
Raesbeck et al (1982) administered indomethacin or placebo to 100 patients undergoing major abdominal surgery; there were five episodes of bleeding in the indomethacin group and none in the placebo group, and they concluded that indomethacin should be used with caution in patients at risk of postoperative bleeding. Unfortunately, they did not mention whether or not their patients also had prophylactic anticoagulation. Previous reports have only dealt with the combined use of NSAIDs and warfarin-like anticoagulants; we have been unable to trace any on the combined use of NSAIDs and heparin.

The major role of heparin is to accelerate the normal rate at which antithrombin III neutralises the proteolytic activities of certain proteases in the coagulation system, but the exact mechanism is unknown. There are great difficulties in establishing the exact plasma heparin level, so the dosage of heparin used has remained empirical (Wessler and Gitel 1979; Salzman et al 1980). The action of heparin on the coagulation system is measured clinically by the whole-blood clotting time and the activated partial thromboplastin time (APTT), but assays are relatively insensitive to heparin and measure the overall influence of the anticoagulant on whole blood or plasma. Moreover, the sites in the clotting system being inhibited are unknown. The most common regime for prophylactic low-dose heparin treatment covering major surgery is 5000 IU twice daily as subcutaneous injections, but there are reports that this dose offers little protection against thrombo-embolic disorders after major orthopaedic surgery (Zucker 1975; Wessler and Gitel 1979).

Baele et al (1983) have shown that treatment with oxametacin also influences the APTT, but no explanation has yet been given for this observation. Therefore, the combination of NSAIDs with heparin might enhance the degree of anticoagulation. The increasing use of NSAIDs in the peri-operative phase of major surgery, where prophylactic treatment with low-dose heparin is the rule, makes it important that clinical trials should establish the safety of this combination.

Our study has shown that the incidence and type of complications after total hip replacement was not changed by the combined treatment with indomethacin and low-dose heparin. There was more postoperative bleeding in the indomethacin group, although this did not reach a significant level. We conclude that combined treatment with indomethacin and low-dose heparin seems to be safe after total hip replacement. Our patients had low-dose heparin in combination with DHE. DHE was added because of the theoretical benefit of venous constrictin in the prevention of deep thrombosis. We found no side effects that could have been ascribed to treatment with DHE.

The period of DHE-heparin treatment in the indomethacin group was significantly shorter than that for the placebo group, because patients receiving indomethacin were mobilised an average of about one day before those on the placebo.

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REFERENCES


