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# No analgesic effect of ibuprofen or paracetamol *vs* placebo for hysterectomies

V. Dahl[a], P. E. Ernø and J. C. Ræder[b]

*Departments of Anaesthesiology, [a]Bærum Hospital and [b]Ulleval University Hospital, Oslo, Norway*

The aim of the present study was to evaluate the postoperative opioid-sparing effect of a pre-operative non-steroidal anti-inflammatory drug (NSAID) (ibuprofen) *vs* paracetamol in a prospective, double-blind, placebo-controlled study. It was also investigated whether the use of ibuprofen or paracetamol would influence the amount of surgical bleeding.

Sixty-six women scheduled for elective open hysterectomy were randomized into one of three groups. All patients received premedication (diazepam 10 mg) and test drugs orally 1 h before the start of anaesthesia: Group 1 ($n=23$) received 800 mg ibuprofen; Group 2 ($n=22$) received 1000 mg paracetamol; and Group 3 ($n=21$) received placebo. General anaesthesia was given with thiopentone-fentanyl-atracurium induction, and maintained with nitrous oxide-isoflurane. Postoperatively, the patients were evaluated hourly during the recovery period, and 1 and 4 days after the procedure.

Postoperative pain was measured by visual analogue scale (VAS), verbal pain score and the need of standardized opioid rescue medication. Intra-operative bleeding was measured, as well as reduction in blood haemoglobin content 24 h and 4 days after the procedure.

No differences were found between the groups in postoperative pain measured by any variable or opioid consumption at any time. The amount of surgical bleeding was equal in the three groups.

Ibuprofen or paracetamol given pre-operatively to hysterectomy patients do not have a postoperative analgesic or opioid-sparing effect. Perioperative surgical bleeding is not influenced by these drugs.

## INTRODUCTION

The role of weak analgesic drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol, in postoperative pain control remains controversial (Dahl & Kehlet, 1991). Previously, it has been shown that ibuprofen given postoperatively to patients undergoing total hip replacement reduced the need of postoperative opioids (Dahl *et al.*, 1995), with a subsequent tendency of reduced nausea and vomiting. In that study, using spinal anaesthesia, post-operative pain was moderate and the need of opioid analgesics was low. In the same study, blood loss was not increased by the use of post-operative NSAID, but in other studies (Engel *et al.*, 1989; Taivanen *et al.*, 1989), increased postoperative bleeding has been demonstrated after NSAID. Paracetamol is associated with few side-effects and does not increase perioperative bleeding. Although paracetamol is thought to possess less analgesic potency than NSAID (Brune, 1986), few clinical studies have compared these drugs and the results are inconclusive (Dolci *et al.*, 1993).

The aim of the present study was to investigate whether weak analgesic drugs have an opioid sparing effect after a procedure with strong post-operative pain, such as hysterectomy. If reduction in pain and postoperative opioid need were present with these drugs, the authors also wanted to

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Correspondence to: V. Dahl, Department of Anaesthesiology, N-1355 Bærum P, Norway.

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study whether there was a difference in analgesic effect between paracetamol and ibuprofen, and whether the amount of surgical bleeding was affected by any regimen.

## MATERIALS AND METHODS

Adult females, American Society of Anesthetists' (ASA) physical status I–III, scheduled for elective hysterectomy were studied in a prospective, randomized, double-blind design, approved by the regional Ethical Committee. Exclusion criteria included: age less than 18 years, a medical history with liver or kidney disease, gastrointestinal bleeding, ulcer, dyspepsia or active inflammatory disease of the intestine, obstructive bronchitis, haematological disease, known allergy to NSAIDs or paracetamol, and the use of an NSAID within the preceding 24 h.

After obtaining informed consent, patients were allocated at random to one of three groups. All patients received identical looking study tablets together with one diazepam 10 mg tablet as premedication 1 h before the start of surgery. Group 1 ($n=23$) received ibuprofen 800 mg, Group 2 ($n=22$) received paracetamol 1000 mg, and Group 3 ($n=21$) received placebo. All patients were given general anaesthesia induced with fentanyl 2 μg/kg i.v. and thiopentone 5.0 mg/kg i.v. Endotracheal intubation was facilitated with atracurium 0.4 mg/kg. Fentanyl 2 μg/kg was repeated at the start of surgery, and further maintenance of anaesthesia was accomplished with isoflurane and 66% nitrous oxide in oxygen. After surgery, muscle relaxation was reversed with glycopyrrulate 0.5 mg and neostigmine 2.5 mg. During the recovery room stay, vital signs [e.g. peripheral oxygen saturation by pulse oximetry ($SpO_2$), systolic blood pressure, heart rate, rate of respiration], level of consciousness, intensity of pain, need of opioid analgesia (ketobemidone i.v.), side-effects and use of other drugs were registered hourly. Pain was estimated using a visual analogue scale (VAS) and a verbal scale. The VAS was a 100 mm non-graded scale, rating from 0 = no pain to 100 = unbearable pain. The verbal scale rated from 1 = no pain to 5 = unbearable pain. The patients were transferred to the gynaecological ward after 6 h. Twenty-four hours and 4 days after the operation, all patients were interviewed and made estimations of the general level of pain using the VAS and the verbal scale. They were also asked about the quality of sleep, ranging from 1 = a good nights sleep to 4 = very bad sleep, and the level of activity, ranging from 1 = activity as normal to 5 = in bed all the time. The need of opioid analgesics and the use of other drugs were registered.

TABLE 1. Pre- and perioperative data

| | Ibuprofen ($n=23$) | Paracetamol ($n=22$) | Placebo ($n=21$) |
|---|---|---|---|
| Age (years ± SD) | 50.2 ± 8.1 | 46.8 ± 7.2 | 49.7 ± 5.9 |
| Weight (kg ± SD) | 68.6 ± 11.9 | 66.7 ± 9.1 | 66.2 ± 8.4 |
| Operation time (min ± SD) | 108 ± 21 | 111 ± 30 | 109 ± 24 |
| Anaesthetic time (min ± SD) | 76.4 ± 22.2 | 81.7 ± 28.6 | 78.7 ± 22.1 |

There are no differences between the groups.

Blood loss was calculated during the perioperative phase by measuring bleeding in drains, suctions and surgical dressings. For postoperative blood loss, the change in haemoglobin content in blood was measured 1 and 4 days after surgery, and compared with pre-operative value. A standardized regimen of perioperative fluid replacement was used, and blood replacement was only used in cases with a perioperative bleeding of more than 1500 ml or a drop in haemoglobin content to less than 80 mg/ml.

## STATISTICS

The Kruskal-Wallis test was used for the non-parametric variables, and ANOVA-variance test was used for the parametric variables. When significant differences were found ($p<0.05$), the groups were compared pairwise by the Mann-Whitney test for the non-parametric results and Student's $t$-test for the parametric results, both with Bonferroni's modification.

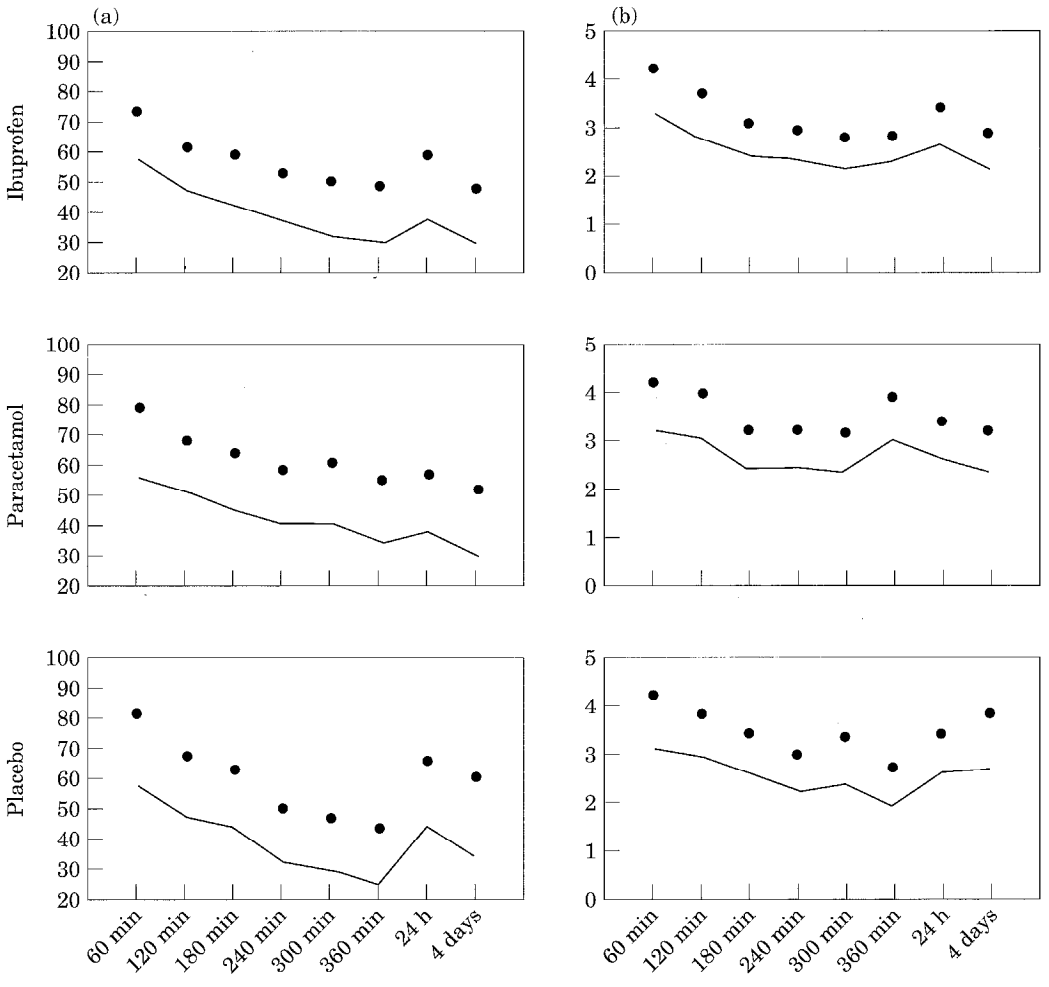


FIG. 1. Postoperative pain on Days 0–4 as estimated by (a) a visual analogue scale from 0 to 100 mm and (b) a verbal scale from 0=no pain to 5=unbearable pain. The pain scores are relatively high with no differences between the groups. Values are mean±SD (●).

## RESULTS

Of the 71 patients recruited for this study, five had to be excluded because of protocol violation. Thus, 66 patients were included in the study. There were no significant differences between the groups in demographic data (Table 1). Other data, such as previous and concomitant diseases, smoking habits, use of alcohol, incidence of headache and travel sickness, were comparable in the three groups (data not shown). Perioperative data, such as time consumption, amount of opioids, blood pressure, heart rate, $SpO_2$ and body temperature were similar between the groups. The postoperative pain scores (VAS and verbal) are shown in Fig. 1 and the use of rescue analgesics is shown in Table 2. There were no statistical differences between the groups. Perioperative bleeding and changes in haemoglobin values postoperatively did not differ between the groups (Table 3).

Heart rate, oxygen saturation, blood pressure, respiratory rate and level of consciousness for the first 6 h postoperatively were within the normal range for all three groups (data not shown). The most common side-effect registered was nausea; 30% of the patients complained of nausea on one or more occasions during the first 4 days postoperatively, without any differences between the groups (Table 4). No other frequent side-

TABLE 2. Use of opioids (ketobemidone) on Days 0–4

| | 60 min | 120 min | 180 min | 240 min | 300 min | 360 min | 24 h | 4 days |
|---|---|---|---|---|---|---|---|---|
| Ibuprofen | 3.37±1.83 | 3.39±0.46 | 1.24±1.30 | 1.39±1.82 | 1.37±1.81 | 0.95±1.08 | 19.6±10.6 | 57.0+15.7 |
| Paracetamol | 4.15±0.59 | 2.93±0.47 | 2.02±2.45 | 1.38±2.16 | 1.33±1.28 | 1.04±1.11 | 21.2±7.88 | 58.8±18.9 |
| Placebo | 4.05±0.40 | 2.71±0.44 | 1.88±1.72 | 1.21±1.71 | 1.05±1.53 | 1.98±2.29 | 18.7±5.9 | 60.1±20.6 |

Values are mg±SD.

TABLE 3. Haemoglobin values and perioperative bleeding

| (g/l±SD) | Pre-operative | Day 1 | Day 4 | Perioperative bleeding (ml±SD) |
|---|---|---|---|---|
| Ibuprofen | 13.1±1.2 | 10.6±1.27 | 10.5±1.3 | 304±156 |
| Paracetamol | 13.1±1.33 | 10.5±1.43 | 10.5±2.0 | 378±280 |
| Placebo | 13.8±1.15 | 11.8±1.43 | 11.5±1.2 | 405±274 |

Haemoglobin values in g/dl. There are no statistical differences between the groups.

effect was registered. The quality of sleep and activity level on Days 1 and 4 were similar in all groups.

TABLE 4. Postoperative nausea (%)

| | | |
|---|---|---|
| Ibuprofen | (*n*=23) | 30 |
| Paracetamol | (*n*=22) | 37 |
| Placebo | (*n*=21) | 20 |

## DISCUSSION

The present study failed to show any benefits or differences in side-effects from pre-operative treatment with either a NSAID or paracetamol. No difference was found in the postoperative pain experience; neither statistically significant differences nor tendencies. One explanation could be that weak analgesics, such as NSAIDs and paracetamol, have too little potency to make any difference in a model with strong postoperative pain. In a previous study (Dahl *et al.*, 1995), the need for rescue opioid (ketobemidone i.v.) in the first 5 h postoperatively was reduced from 6.5 to 4.5 mg when an NSAID was added. In the present study, the average need of opioid (ketobemidone i.v.) for the same period was much higher (11–12 mg), thus indicating that the pain experienced was stronger. The lack of differences between the groups makes it impossible to evaluate the relative potency of paracetamol compared to NSAID. Thus, this important question remains unanswered and further investigations are necessary. Another possibility for the lack of differences could be a lack of sensitivity in the present method to evaluate pain. However, the same methods were used in one of the authors' earlier studies where significant differences were found in both pain experience and opioid consumption after primary hip arthroplasty (Dahl *et al.*, 1995). The goal of any postoperative pain treatment is to reduce pain. An analgesic treatment unable to demonstrate changes in VAS, verbal pain scale or need of rescue medication is of little clinical benefit. In a recent study, Friedman *et al.* (1996) found no analgesic effect of ketorolac in reducing pain after prostatectomy. The present study supports this result.

Non-steroidal anti-inflammatory drugs have significant effects on the blood platelets by inhibiting cyclo-oxygenase and thus the production of thromboxane ($TXA_2$) in the platelets. Thromboxane is a potent vasoconstrictor and platelet aggregator (Lands, 1985). Although NSAIDs have been shown to prolong the primary bleeding time (Power *et al.*, 1990), it is still controversial whether this effect has any clinical relevance (Laitinen *et al.*, 1992; Nuutinen *et al.*, 1993). In the present study, no alteration in the perioperative bleeding was found between the groups as measured by the amount of blood loss during the operation (blood volume in suction device

and in swabs) and haemoglobin reduction (Table 3). The present results support the statements of other investigators, concluding that NSAIDs can be used safely in surgical procedures (Dahl & Kehlet, 1991) where efficient surgical haemostasis and wound closure are possible.

## CONCLUSION

Pre-operative ibuprofen or paracetamol does not have a postoperative analgesic or opioid-sparing effect after hysterectomy. Neither ibuprofen or paracetamol alters the perioperative blood loss.

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