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Effectiveness of naproxen in laparoscopic sterilization: a double blind randomized placebo controlled study

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Effectiveness of naproxen suppositories on ambulation was studied following laparoscopic sterilization. In a double-blinded randomized placebo study, 20 patients received 500 mg naproxen suppositories and 20 patients placebo suppositories. Postoperatively 10 naproxen patients and 11 placebo patients reported high pain scores, indicating severe pain and requiring opiates. Times to reach street fitness were equally prolonged in both groups. Most patients in both groups required 3 days to resume normal duties and post-discharge weakness was a common complaint. Our conclusion was that premedication with naproxen 500 mg suppositories in day-case laparoscopic sterilization therapeutically behaves like other commonly used non-steroidal anti-inflammatory drugs (NSAIDs) and does not substantially contribute to ambulation.

Key words: Anaesthesia: day-case/ambulatory, analgesics: naproxen, procedure: laparoscopic sterilization/ Fallope rings

Introduction

Prostaglandins released from traumatized ischaemic fallopian tubal tissue are assumed to play a role in the high incidence of lower abdominal cramp-like pains following laparoscopic sterilization under general anaesthesia (GA)[1]. Consequently prescribing non-steroidal anti-inflammatory drugs (NSAIDs) would seem to be indicated. However reports as to the efficacy of these agents have yielded inconsistent results. When using NSAIDs beneficial effects on postoperative pain reduction, reduced need for postoperative opiates and rapid ambulation have been claimed[2,3], while similar results could not be demonstrated in other studies[4,5]. In the above quoted studies which produced favourable results, naproxen was the NSAID used, suggesting clinical effectiveness for this agent.

Additionally, its good safety record and its long duration of action would seem to make naproxen a suitable analgesic in this category of day surgery patients.

We therefore evaluated the effects of premedication with naproxen 500 mg suppositories on postoperative and post-discharge outcome in 40 patients after laparoscopic sterilization with Fallope rings.

Patients and methods

Forty ASA grade I patients, scheduled for day-case laparoscopic sterilization under GA, participated in this institutionally approved placebo-controlled, randomized double-blind study. Written informed consent was obtained from each subject before entering the study.

Before surgery patients were familiarized with pain scales to be used both after awakening in the Post-Anaesthesia Care Unit (PACU) and when at home. Pain measurement was by verbal response to a 10 cm visual analogue scale (VAS) with 0 indicating no pain on the left at the start and 10 indicating agonizing pain on the right end of the scale[7].

During their stay in the hospital pain scores were assessed by an observer blinded to patient allocation. Patients were allocated by random numbers to two treatment groups. One hour before transport to the operating theatre, each patient had a suppository placed, containing either 500 mg naproxen ($n = 20$) or placebo ($n = 20$). Study medication was supplied by Sarva Syntex (Rijswijk, the Netherlands) and randomization was achieved

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with computer-assisted generation of random numbers in the hospital pharmacy, where study medication (identical-looking suppositories) was put into consecutively numbered coded envelopes.

The rectal route for drug absorbtion was selected to avoid gastrointestinal disturbances and fewer mucosal lesions are produced by naproxen administered as suppositories[14]. Induction of anaesthesia was with propofol and sufentanil, 10 or 30 μg, depending on body weight. Intubation and ventilation were with vecuronium. Anaesthesia was maintained with nitrous oxide in 40% oxygen and propofol. If necessary, residual neuromuscular blockade was reversed with neostigmine/atropine. All patients received 20 ml kg^{-1} iv Ringer's solution containing dextrose[8]. For laparoscopy a two-puncture technique was used and pneumoperitoneum was induced with carbon dioxide and Falope rings were applied in all cases.

Pain scores were recorded at 30, 60 and 120 min after arrival in the recovery ward in the outpatient step-down unit. On patient's demand and/or staff discretion 7.5–10 mg s.c. morphine sulphate was administered. If patients were also complaining of lower abdominal cramps, additional naproxen was available.

Discharge was considered if all vital signs had remained stable and patients could void, were alert, could dress and had no symptoms of nausea. Time from induction of anaesthesia up to time of fitness for discharge was recorded as T = street fitness. On discharge all patients were given two naproxen suppositories to use at home at their own discretion. If pains at home were still not completely relieved, patients could take additional acetaminophen 1000 mg. The following morning patients were contacted by telephone and enquiries were made as to the intake of analgesics and whether they had noticed any other unusual signs or symptoms.

Within a week after discharge, each patient was asked to report after how many days they had felt able to resume normal duties and whether they had noticed other unusual symptoms they wished to report.

Statistical analysis

Between-group differences were analysed with the unpaired Student's *t*-test (two-tailed) and comparison of pain scores between groups with the Wilcoxon's rank sum test (two-tailed). Results are expressed as medians with range[10]. Differences between proportions were analysed with the χ^2 or Fisher's exact test where appropriate. $P < 0.05$ indicated significance.

Results

Demographic and logistic data are presented in Table 1, showing similarity for both groups of patients. There was no protocol deviation and all patients who were initially recruited completed the study.

Analysis of our data showed that postoperatively, in the placebo group as well in the naproxen premedicated group, patients reported equally high pain scores, which could be considered severe (Figure 1)[7]. There were also no detectable differences in postoperative consumption of analgesics and in order to include VAS ratings down to around three, 13 placebo patients required opiates compared to 11 patients in the naproxen group. Fourteen patients in the placebo group and 11 patients in the treatment group were given additional naproxen postoperatively. There were no differences between both groups in times to reach street fitness and three patients in each group required overnight admission (Table 1).

When comparing these data, no significant differences could be detected (Table 2). On the morning following surgery VAS scores in both groups of patients had returned to values around two[6].

In relation to preoperative information supplied to the patients, out of 40 subjects studied, 18 placebo patients and 15 naproxen treated patients commented that the procedure experienced was much worse than had been expected, and 18 naproxen treated patients compared to 14 placebo patients could resume normal duties on the fourth postoperative day. Unwanted side effects are presented in Table 3.

Table 1. Characteristics of the study population*

	Placebo	*Naproxen*	*P*
Age (yr)	34.3 ± 4.7	36.1 ± 5.2	ns
Height (cm)	166 ± 7.6	167 ± 7.6	ns
Weight (kg)	67.4 ± 9.5	68.5 ± 13.6	ns
Duration of surgery (min)	17 ± 5.8	16 ± 4.6	ns
T = Street fitness (min)	370 ± 105	320 ± 94	ns
Number of admissions	3	3	ns

*Values are means ± SD. P, probability; ns, not significant (Student's *t*-test).

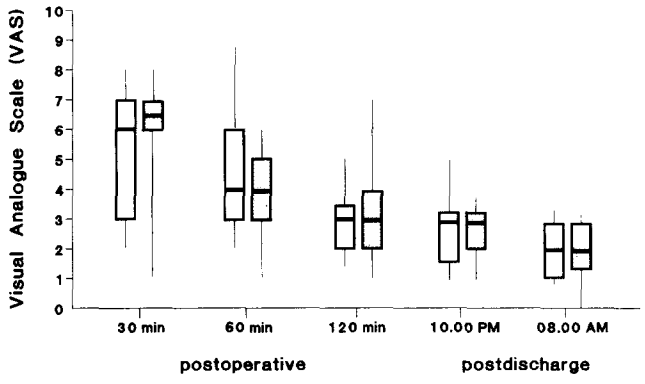

Figure 1. Distribution of pain scores at 30, 60, and 90 min postoperatively and after discharge. Postoperative pain scores plotted on the visual analogue scale (VAS). Because the data are not normally distributed, box plots are used; the box representing values in the second and third quartiles. The median value is represented by the horizontal bar in the box. Both upper and lower values are shown above and below each box[9]. Open boxes represent the naproxen group and shaded boxes represent the placebo group. Wilcoxon rank sum test; $P < 0.05$ indicating significance.

Table 2. Number of patients requiring analgesics in the postoperative period

	Placebo (n = *20*)	*Naproxen* (n = *20*)*
Naproxen	4	2
Opiates	3	3
Naproxen + opiates	10	9
No analgesics	3	6

*No statistically significant differences were obserbed between both groups.

Discussion

Results of this study indicate that following day-case laparoscopic tubal ligation with Fallope rings, patients premedicated with naproxen suppositories reported equally high postoperative pain scores as placebo patients, with roughly half of the patients in each group requiring parenteral opiates. Our data are in agreement with earlier studies, reporting insufficient postoperative analgesia following administration of other commonly used NSAIDs[4,5], where indomethacin and diclofenac were the agents used.

In relation to its pharmacological profile, there seems to be no indication to assume better quality analgesia for naproxen compared to these other agents[14]. Clinically this should not be considered as entirely unexpected, because both fallopian tubes are intraperitoneal structures and acute disruption of their integrity constitutes an acute phase 1 nociceptive stimulus, in which NSAIDs are likely to be ineffective[11].

On the following day many patients in both groups were still complaining of lower abdominal discomfort and general weakness (Table 3), sometimes lasting several days, which might be compatible with phase 2 hyperalgesia[11,12].

As fitness for discharge in both groups could often only be considered late in the afternoon, coupled with an overall overnight admission rate of 15%, it is unlikely that premedication with naproxen suppositories in the population that we studied had contributed substantially to rapid ambulation.

It could be argued that compared to orally administered formulations of naproxen sodium[15], longer times will be needed to reach therapeutic levels, due to delayed resorbtion from suppositories. With tablets too, lower plasma levels of the active drug component could result from delayed gastric emptying times in these preoperatively otherwise unpremedicated anxious patients.

Although effectiveness of preoperative naproxen sodium tablets in this category of patients was reported, we choose to administer rectal formulations to avoid direct mucosal irritation, possibly leading to a higher incidence of postoperative nausea which is an undesirable side effect in day-care patients. Besides, administering suppositories long before induction of anaesthesia should provide for effective blood concentrations at the time of surgery when Fallope rings are placed.

It is possible that a relationship exists between the reported high pain scores and increased subjective assessment of postoperative pain after gynaecological surgery[13] in patients who may be emotionally ill-prepared for inconvenience after sterilization, as patients were generally unaware of the possibility of the appearance of severe postoperative pains. Also considerable variation exist between individuals as to pain perception, explaining the extremes in VAS scores as depicted on the box plots (Figure 1).

Application of Fallope rings has been implicated as being more painful than tubal occlusion with Filshie clips and as such could have contributed to reporting of higher self-assessed pain scores. However in one study, using indomethacin, this could not be demonstrated[4].

In agreement with results which appeared in similar previously published studies where other commonly prescribed NSAIDs were used, we concluded that therapeutic benefits to be derived from perioperative administration of 500 mg naproxen suppositories as the main analgesic agent in laparoscopic tubal ligation with Fallope rings, are only modest.

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Table 3. Number of patients experiencing side effects

	Placebo (n = *20*)	*Naproxen* (n = *20*)*
Nausea, vomiting	6	6
Tinnitus, headache, dizziness	4	6
Feelings of instability, tiredness, weakness	11	8
Shoulder pain	10	7
Normal duties at day 4 postoperatively	14	18

*No statistically significant differences were observed between both groups.

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