

The effect of dextromethorphan, alone or in combination with ibuprofen, on postoperative pain after minor gynaecological surgery

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Background: Experimental studies have demonstrated that peripheral tissue injury may lead to hyperexcitability of nociceptive neurones in the dorsal horn, in part mediated by N-methyl-D-aspartate (NMDA)-receptor mechanisms. Sensitisation of dorsal horn neurones may be an important contributor to postoperative pain. The aim of the present study was to investigate the effect of the NMDA-receptor antagonist dextromethorphan on pain after minor gynaecological surgery, and to evaluate a potential additive effect with ibuprofen.

Methods: In a double-blind, placebo-controlled study, 100 patients scheduled for elective termination of pregnancy were randomised to receive placebo, oral ibuprofen 400 mg, oral dextromethorphan 120 mg, or a combination of ibuprofen 400 mg and dextromethorphan 120 mg, 1 h before surgery. Pain and analgesic requirements were assessed 0.5, 1 and 2 h after operation. **Results:** We observed no effect of dextromethorphan on visual analogue scale (VAS) pain scores or analgesic consumption, and no additive or synergistic analgesic effects between ibuprofen and dextromethorphan. Ibuprofen reduced pain scores com-

pared with placebo, and analgesic consumption compared with both placebo and dextromethorphan. The combination of ibuprofen and dextromethorphan increased preoperative nausea compared with both placebo and ibuprofen, whereas no statistically significant side effects were observed with dextromethorphan alone.

Conclusion: No analgesic effects of oral dextromethorphan 120 mg on pain after surgical termination of labour, and no additive analgesic effects when combined with ibuprofen 400 mg, were observed. Ibuprofen reduced both VAS pain scores and analgesic consumption compared with placebo.

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EXPERIMENTAL studies have demonstrated that peripheral tissue injury may lead to hyperexcitability of nociceptive neurones in the dorsal horn, in part mediated by N-methyl-D-aspartate (NMDA)-receptor mechanisms (1). Injury-induced sensitisation of dorsal horn neurones has been implicated as an important contributor to both acute and chronic pain states (2).

Dextromethorphan is a noncompetitive (NMDA)-receptor antagonist known to inhibit wind-up and nociceptive responses of dorsal horn neurones (3). Experimental studies further indicate that NMDA-receptor antagonists may potentiate the effect of various analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) (4–6).

In human pain models, dextromethorphan was shown to attenuate temporal summation of secondary pain (7, 8), and to reduce the magnitude of secondary hyperalgesia after a burn injury (9). It has been re-

ported that the side effects of dextromethorphan are rare and mostly unimportant and that the drug has a wide margin of safety (9, 10). Together, these findings suggest that dextromethorphan may be a potentially useful remedy in postoperative pain treatment.

Results from previous clinical studies of postoperative pain are conflicting, however, possibly in part related to administration of insufficient doses of the drug (11–15). The aim of the present study was to investigate the effect of high-dose oral dextromethorphan (120 mg) on pain after minor gynaecological surgery, and to evaluate a potential additive or synergistic effect with ibuprofen.

Patients and methods

We studied women more than 18 years of age and with less than 13 weeks of gestation, scheduled for elective termination of pregnancy under general anaesthesia.

Informed written consent was obtained from all patients and approval was obtained from the local Ethics Committee and the Danish National Board of Health. Patients were recruited from the Department of Gynaecology, Skejby Sygehus, Aarhus University Hospital during the period November 1997 to May 1998. Excluded patients were replaced until 100 data sets, 25 for each treatment group, were available for analysis. Before surgery, patients were asked to rate their pain during menstruation on a visual analogue scale (VAS, 0 mm=no pain, 100 mm=worst pain imaginable). Only women with a VAS score ≥ 30 were included. Patients with a history of drug or alcohol abuse, chronic pain or daily intake of analgesics, and those unable to cooperate, were not included.

The study was double-blind, randomised (computer generated random numbers) and placebo-controlled. The study drugs (identical tablets of dextromethorphan 120 mg, ibuprofen 400 mg or placebo) were prepared by the pharmaceutical company (Nycomed Dak A/S, Roskilde, Denmark) in identical containers, marked with the name of the project, the investigator's name and the consecutive patient numbers. For each patient number, two containers were prepared, one containing either dextromethorphan 120 mg or placebo, the other either ibuprofen 400 mg or placebo. The combinations received by the patients were either placebo+placebo (PLA), ibuprofen 400 mg+placebo (IBU), dextromethorphan 120 mg + placebo (DEX), or ibuprofen 400 mg + dextromethorphan 120 mg (IBU/DEX).

The patients were scheduled to receive study drug between one and two hours before surgery. No other premedication was given. Anaesthesia was induced with 1 mg alfentanil and propofol. Propofol was used for maintenance of the anaesthesia and patients received a mean of propofol 5 mg/kg. Patients breathed pure oxygen spontaneously, and were ventilated only

if necessary. Cervical dilation and a vacuum aspiration was done and the cavity was curetted.

Postoperatively, pain scores (VAS, 0 mm=no pain, 100 mm=worst pain imaginable), were assessed by patients at 0.5, 1 and 2 h after operation. Patients who experienced a VAS score of ≥ 30 were treated with paracetamol 1 g orally in combination with morphine 2.5 mg intravenously. Pain was reassessed after 15 min, and if VAS score was still above 30, another dose of morphine 2.5 mg was given intravenously. Thereafter, morphine 2.5 mg intravenously was administered on patients' request until VAS was ≤ 30 .

Sedation (VAS, 0 mm=fully awake, 100 mm=almost sleeping) and nausea (0=none, 1=slight, 2=moderate, 3=severe) rated by the patients, and number of episodes of vomiting, were recorded immediately before surgery, and at 0.5, 1 and 2 h after operation.

Statistical analysis

The sample size was based on a power calculation which showed that 24 patients per group were necessary to achieve 80% power to detect a difference of 20 mm (VAS) in pain scores between patients treated with dextromethorphan compared with placebo, with $\alpha < 0.05$ (two-tailed). Based on these values, we decided to include 25 patients in each group.

Data are presented as medians, with upper and lower quartiles. Statistical analyses were performed with Fisher's exact test, and the Mann-Whitney and the Kruskal-Wallis rank sum tests for unpaired data, where appropriate. If multiple testing was performed, significant *P* values were corrected with a Bonferroni test for repeated measurements.

Results

Of 105 patients included, 5 were excluded, leaving 25 patients in each study group. The reasons for ex-

Table 1

Demographic and operative data. Medians, with upper and lower quartiles.

	Placebo	Ibuprofen 400 mg	Dextromethorphan 120 mg	Ibuprofen 400 mg + Dextromethorphan 120 mg
N	25	25	25	25
Age (yr)	23 (22–31)	25 (22–32)	26 (23–31)	27 (23–32)
Height (cm)	170 (166–172)	169 (164–172)	168 (165–170)	168 (164–170)
Weight (kg)	62 (58–70)	58 (55–61)	63 (58–66)	62 (56–68)
Gestation weeks	8 (7–8)	8 (7–8)	8 (7–8)	8 (7–8)
Number of patients receiving vaginal prostaglandins	2	1	1	3
Time from test medication to surgery (min)	75 (65–90)	75 (65–100)	85 (70–95)	80 (65–95)
Duration of surgery (min)	10 (10–10)	10 (10–11)	10 (7–10)	10 (7–11)

No significant differences between groups.

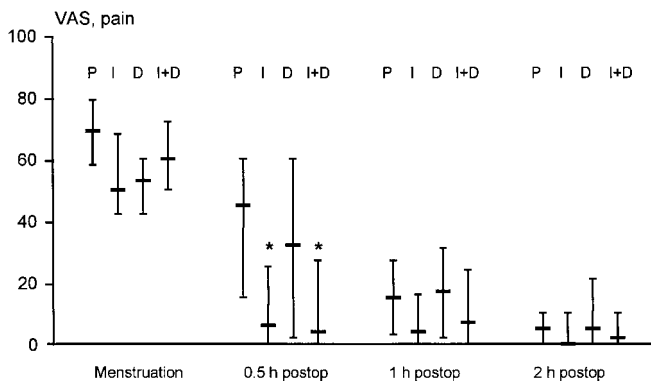


Fig. 1. Pain during menstruation, and 0.5, 1, and 2 h after surgery. During menstruation, and 1 h and 2 h after surgery, no significant differences between groups (Kruskal-Wallis test, with Bonferroni's correction for multiple comparisons, $P > 0.05$). At 0.5 h after surgery, significant differences between groups, $P = 0.003$ (Kruskal-Wallis test). * $P < 0.05$, compared with placebo. P=placebo; I=ibuprofen 400 mg; D=dextromethorphan 120 mg. Median (upper and lower quartiles).

clusions were: four due to administration of medication not approved in the protocol; one due to perforation of the uterine cavity. Seven patients received vaginal prostaglandins for cervical dilatation, equally distributed between the treatment groups. Patient characteristics and operative data are shown in Table 1.

Pain scores and analgesic consumption

No significant differences were found between groups for VAS scores during menstruation. After operation, there were no differences between VAS scores in patients receiving DEX versus PLA, or IBU versus IBU/DEX at any time of assessment (Fig. 1). Significant lower VAS scores were observed in patients receiving IBU or IBU/DEX compared with PLA at 0.5 h, but not at 1 h or 2 h after operation (Fig. 1).

There were no significant differences in morphine consumption between patients receiving DEX versus PLA, or IBU versus IBU/DEX. Patients receiving IBU needed significantly less morphine than patients receiving PLA and patients receiving DEX (Table 2).

Side effects

There were no significant differences in the level of sedation (Fig. 2) at any time of assessment, and only one patient, in the IBM/DEX group, vomited. Pre-operatively, patients receiving IBU/DEX experienced significantly more nausea than patients receiving PLA and patients receiving IBU (Table 2). No differences in nausea were observed after operation. No other side effects were noted.

Discussion

We observed no effect of oral dextromethorphan 120 mg on VAS pain scores or analgesic consumption, and no additive or synergistic analgesic effects between dextromethorphan 120 mg and ibuprofen 400 mg in patients scheduled for surgical termination of pregnancy. Ibuprofen reduced VAS scores compared with placebo, and analgesic consumption compared with both placebo and dextromethorphan. The combination of ibuprofen and dextromethorphan increased preoperative nausea compared with both placebo and ibuprofen, whereas no statistically significant side effects were observed with dextromethorphan alone.

It has been suggested that sensitisation of central nociceptive pathways may contribute to dysmenorrhoeic pain (16). Our results demonstrate a sufficient internal sensitivity, with a significant effect of ibuprofen on pain and analgesic requirements. In a recent systematic review of minor analgesics in pri-

Table 2

Pain medication and nausea during the first two hours after surgery.

	Placebo	Ibuprofen 400 mg	Dextromethorphan 120 mg	Ibuprofen 400 mg+ Dextromethorphan 120 mg
N	25	25	25	25
Number of patients receiving paracetamol+morphine	17	9*	16	10
Number of doses of morphine requested (2.5 mg i.v.) ^a	26	11* [#]	29	17
Number of patients with nausea ^b	7	6	12	15* [§]

* $P < 0.05$ vs placebo.

[#] $P < 0.05$ vs dextromethorphan.

[§] $P < 0.05$ vs ibuprofen.

^a Kruskal-Wallis test between the groups $P = 0.05$.

^b Kruskal-Wallis test between the groups $P = 0.008$.

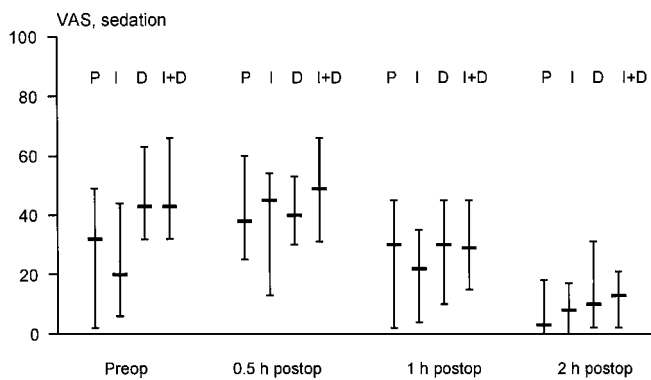


Fig. 2. Sedation (VAS, 0=fully awake, 100 mm=almost sleeping) immediately before operation, and 0.5, 1, and 2 h after surgery. No significant differences between groups. P=placebo; I=ibuprofen 400 mg; D=dextromethorphan 120 mg. Median (upper and lower quartiles).

mary dysmenorrhoea (17) the authors conclude that, based on efficacy and absence of common adverse effects, ibuprofen is probably the analgesic treatment of choice in this condition. From our results it may be concluded that ibuprofen seems equally effective after surgical termination of pregnancy. In fact, it was not possible to evaluate a possible potentiating effect of dextromethorphan on VAS pain scores from our data, since pain scores with ibuprofen were consistently very low after operation. However, 9 of 25 patients receiving ibuprofen needed rescue analgesic, and a power calculation showed that our study had 80% power to detect a 45% reduction in this need, with $\alpha=0.05$.

Results from previous clinical studies with dextromethorphan in postoperative pain are contradictory. Thus, premedication with oral dextromethorphan 45 mg reduced pain and analgesic requirements for seven days after tonsillectomy in adult patients in one study (11), whereas no analgesic effects after premedication with 1 mg/kg before adenotonsillectomy in children were observed in another study (15). Oral dextromethorphan 27 mg, administered on the night before and again 1–2 h before operation, and 8, 16 and 24 h after operation, did not reduce pain or PCA morphine consumption after total abdominal hysterectomy (13). Oral dextromethorphan 60 mg the night before and again 1 h before surgery reduced intra- but not postoperative morphine requirements after abdominal laparotomy (12). Finally, intramuscular dextromethorphan 40 mg, 30 min before skin incision, reduced “worst pain score” and 48 h opioid requirements after laparoscopic cholecystectomy (14). We have observed a 30% reduction in morphine consumption during 0–4 h postoperatively with a single dose of oral dextromethorphan 150 mg, administered

1 h before abdominal hysterectomy, compared with placebo (18).

In a recent study in human volunteers, dextromethorphan 120 mg, but not 60 mg, was capable of reducing secondary hyperalgesia and thus central sensitisation after a burn injury (9). No important side effects were observed in that study (9). Based on these findings, we speculated whether the rather small doses (≤ 60 mg) applied in the published studies of postoperative pain might explain the opposing and often negative results in these studies.

Oral dextromethorphan 120 mg was without effects, however, in the present study. As the most possible explanation for this finding we suggest that pain after surgical termination of pregnancy is mostly due to local inflammation, and that central sensitisation of dorsal horn neurones only plays a minor role, if any, in this condition. Another explanation might be that the primary effect of dextromethorphan is a potentiation of opioid analgesics (19), and not an analgesic effect per se. It must be emphasised, though, that the analgesic effects of NMDA-receptor antagonists in general (20), and of dextromethorphan in particular, in various postoperative pain states awaits clarification.

In conclusion, we observed no analgesic effects of oral dextromethorphan 120 mg on pain after surgical termination of labour, and no additive analgesic effects when combined with ibuprofen 400 mg. Ibuprofen reduced both VAS pain scores and analgesic consumption compared with placebo.

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