

# A double blind, randomised trial to compare the analgesic effect of oral premedication with paracetamol, diclofenac, or diclofenac and paracetamol, on postoperative pain following surgical suction termination of pregnancy

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## Abstract

**Objectives:** The aim of this study was to determine whether a combination of paracetamol and diclofenac provided a more effective analgesic premedication than paracetamol, or diclofenac alone for the treatment of postoperative pain following surgical suction termination of early pregnancy.

**Methods:** A double blind, prospective trial, involving 60 patients randomized to receive either paracetamol (1 g) and placebo, diclofenac (50 mg) and placebo, or diclofenac (50 mg) and paracetamol (1 g) orally, prior to surgical termination of pregnancy. Intraoperative management was standardized. Peak pain was the primary end point. Pain scores were recorded immediately postoperatively, and at 2 and 4 h. Secondary end points were nausea, sedation, intraoperative blood loss, supplementary postoperative analgesic use, and delayed hospital discharge.

**Results:** There was no statistically significant difference in peak pain between the three groups ( $P=0.6$ ).

**Discussion:** The co-administration of prophylactic oral analgesic premedication with diclofenac and paracetamol did not result in a reduction in pain scores when compared to either diclofenac or paracetamol administered alone.

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**Keywords:** Paracetamol; Diclofenac; Analgesia; Postoperative pain; Prevention and control

## 1. Introduction

Suction termination of pregnancy is a commonly performed day-case surgical procedure, often resulting in mild to moderate lower abdominal postoperative pain. Persistent postoperative pain is both unpleasant for the patient, and may lead to delayed discharge.

Analgesic premedication with paracetamol in combination with diclofenac or diclofenac alone is routine practice in our hospital, and in many other centers. The evidence for the analgesic efficacy of paracetamol and NSAIDs administered

alone is poor, but no evidence exists to determine the relative efficacy of a combination of NSAIDs and paracetamol in this common clinical situation. Our hypothesis was that the combination of diclofenac and paracetamol would produce a clinically significant reduction in analogue pain scores.

## 2. Materials and methods

Approval was obtained from the Local Research Ethics Committee. Written informed consent was gained preoperatively from 60 consecutive female patients scheduled for elective surgical termination of pregnancy (STOP) over a 6-month period in a large teaching hospital. Inclusion criteria

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Table 1  
Patient demographics

	Group A: paracetamol ( <i>n</i> = 20)	Group B: diclofenac ( <i>n</i> = 20)	Group C: both ( <i>n</i> = 18)
Age (year)	27 (8)	27 (8)	24 (6)
Weight (kg)	66 (11.3)	67 (10.7)	67 (6.3)
Time from premed to surgery (min)	79 (37)	89 (35)	76 (36)
Duration of surgery (min)	12 (4)	11 (5)	11 (4)
Had misoprostil ( <i>n</i> )	10 (50%)	12 (60%)	10 (56%)
IUCD implanted ( <i>n</i> )	7 (35%)	8 (40%)	4 (22%)

Data expressed as mean (standard deviation) or number (percentage of total).

were age 16–35 years and American Society of Anesthesiologists (ASA) class I or II. Exclusion criteria were a history of allergy to any of the medications used in the study, asthma, peptic ulcer disease, chronic analgesic use, or necessity for tracheal intubation.

A computer-generated randomization list with three groups was drawn up by the hospital pharmacy department, who prepared sealed, numbered packages based upon this list. Each paper package contained an opaque plastic container, containing three tablets, with Vitamin C being used as a placebo. Tablet preparations were chosen for their similar appearance. The packages contained paracetamol 1 g and placebo (Group A), diclofenac 50 mg and placebo (Group B), and paracetamol 1 g and diclofenac 50 mg (Group C). Women were allocated the next available number on entry to the trial, and prior to surgery the ward nurse gave the package to the patient with a small glass of water. The code was revealed to the researchers only once recruitment and data collection were complete.

Anaesthesia was induced with propofol 2–4 mg kg<sup>-1</sup>, following intravenous fentanyl 100 µg and ondansetron 4 mg. A laryngeal mask was inserted, and anaesthesia maintained with isoflurane in nitrous oxide and oxygen, with spontaneous respiration. Duration of surgery, blood loss, and the volume of intravenous fluid given were recorded. Nursing staff administered misoprostol gel vaginally, 1 h preoperatively, to patients who had not previously delivered vaginally. Patients who requested an intrauterine contraceptive device (IUCD) preoperatively had a Mirena coil (Schering Health, Berlin, Germany) placed after the evacuation of the uterus. No oxytocic drugs were administered to any patient during the study.

Analogue pain scores from 0 (no pain) to 10 (worst pain imaginable), and the incidence of nausea and vomiting were assessed immediately postoperatively, and after 2 and 4 h. Tramadol 50 mg and dihydrocodeine 30 mg were prescribed for all patients as required for postoperative analgesia. These were administered at the discretion of the nursing staff to patients with pain scores of three or greater. Patients who reported nausea or vomited postoperatively were administered prochlorperazine 12.5 mg intramuscularly. Patients were allowed tea and toast postoperatively in the recovery ward. The majority of patients were discharged at 4 h following surgery, but if discharge was delayed, then the reason for this was recorded. Potential confounding variables, such as age, weight, use of misoprostol gel, or insertion of an IUCD were recorded.

Prior to starting the study, we considered that a difference in pain scores of two or more would be clinically significant. Power calculation demonstrated that in order to detect a difference of this magnitude, with an  $\alpha$ -error of 0.05 and a power of 0.85, we would require 20 patients in each group. Subsequent analysis confirmed that the study was powered to detect this difference.

### 3. Results

Two patients were excluded from the analysis. One vomited several minutes after swallowing the tablets, and one declined the procedure after administration of the tablets. Table 1 contains the remaining 58 patients' characteristics, and Table 2 contains the results. The highest pain score reported by each patient during the postoperative period was recorded as the 'peak pain', and this data was regarded as not being normally distributed. The data were analyzed using the Kruskal–Wallace test, analysis of variance, or the Chi-square method as appropriate. Patient characteristics were well matched between treatment groups. Analysis of two potential confounding variables revealed no significant difference in peak pain scores between those patients who received misoprostol and those who did not (median 2.0 versus 3.0, respectively,  $P=0.21$ ) and those patients who received an IUCD and those who did not (median 2.0 versus 3.0,  $P=0.91$ ).

There was no statistically significant difference in peak pain scores or requirement for rescue analgesia between the three treatment groups ( $P=0.6$ ). A non-significant association was noted between premedication with diclofenac, and nausea and requirement for supplementary anti-emetics. Delayed discharge was only noted in one patient, a Group C patient, as a result of nausea.

### 4. Discussion

The existing literature contains little evidence for the efficacy of NSAIDs used as analgesic prophylaxis in minor gynecological surgery. Jacobsson et al. [1] demonstrated significantly reduced pain with intramuscular diclofenac 75 mg, but not oral diclofenac 50 mg. This result may have been affected by the use of retrospective assessment of pain, insufficient time for absorption of the oral preparation prior to

Table 2  
Primary and secondary endpoints

	Group A: paracetamol (n = 20)	Group B: diclofenac (n = 20)	Group C: both (n = 18)	P-value
Peak pain				
Mean	3.2	3	2.6	
Median	2.5	3	2	0.60
25th–75th centiles	1–5.0		2.0–4.5	
Range	0–8.0		0–8.0	
Rescue analgesia required				
(n)	13 (65%)	10 (50%)	9 (50%)	0.63
Nausea (n)	2 (10%)	4 (20%)	4 (22%)	0.56
Anti-emetics required (n)	0 (0%)	2 (10%)	3 (17%)	0.18
Blood loss (mL)	210 (118)	277 (211)	249 (135)	0.44

Number of patients (percentage of total) for 'rescue analgesia', anti-emetics, and nausea, and mean (standard deviation) for blood loss.

surgery, and lack of blinding. Hein et al. [2] demonstrated a reduction in pain with oral lornoxicam 8 mg. However, in this study, rescue analgesic requirement was no different from placebo and the unorthodox method of analyzing pain could have amplified a small clinically insignificant difference.

A literature search revealed no evidence for the efficacy of prophylaxis with paracetamol in these circumstances. Two studies were unable to demonstrate any statistically significant benefit from the use of paracetamol [3,4]. However, Cade et al. utilized an insensitive measure of pain (i.e. pain or no pain) and Hein et al. administered the paracetamol rectally at the end of surgery, resulting in an inadequate time for absorption and reduced bioavailability. We utilized the oral route, which has greater bioavailability and less variability than the rectal route [5], and we allowed adequate time for absorption [6]. In our study, premedication with diclofenac resulted in no significant reduction in postoperative pain, when used either in place of, or in addition to paracetamol. This result is perhaps surprising, given the accepted efficacy of NSAIDs in treating moderate pain [7]. Possible explanations for this lack of effect include drug pharmacokinetics, dosage, and severity of pain. We would expect from the available literature on the pharmacokinetics of diclofenac [8], that its analgesic effect would be near its peak immediately postoperatively, having been administered 1–2 h previously. Diclofenac 50 mg has been shown by systematic review to be an effective dose for the treatment of moderate to severe postoperative pain [7] and increasing the dose to 100 mg only minimally increases efficacy (number needed to treat 2.3 versus 1.8, respectively). In addition, systematic review has shown a lack of evidence for differences in analgesic efficacy between routes of administration for NSAIDs [9]. It is possible that the lack of demonstrable effect of diclofenac used as prophylaxis is due to the fact that only 18 (31%) of the patients reported moderate to severe pain [10], while most experienced only mild discomfort which was self-resolving and did not require analgesic treatment.

Given the lack of positive findings, it would be prudent to consider the sensitivity of the experimental model, and in particular whether the use of fentanyl at induction may have affected the results. It is common practice to utilize a short acting opioid to achieve balanced anaesthesia, and we ad-

ministered fentanyl 100 µg to reflect this, thereby allowing the results to be applicable to routine anaesthetic practice. In addition, the available evidence suggests that an intraoperative bolus dose of fentanyl has no effect on postoperative pain scores or postoperative analgesic requirements [11,12]. Given the routine use of paracetamol as an analgesic premedication in our hospital, it was considered unethical to use a placebo control in this study. In summary, we utilized a well-validated measure of acute pain, and an adequate number of patients and no clinically or statistically significant difference was found between the treatment groups.

The routine use of prophylactic analgesia for surgical termination of pregnancy is widespread. We have demonstrated that there was no clinically significant difference between the treatment groups with respect to the primary outcome. The results of this study do not support the prophylactic co-administration of oral analgesic premedication with diclofenac and paracetamol as the combination confers no significant clinical benefit over either paracetamol or diclofenac alone.

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