

# The postoperative analgesic effects of low-dose gabapentin in patients undergoing abdominal hysterectomy

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**Objective.** Clinical studies have suggested that gabapentin may produce analgesia in postoperative patients. The aim of this study was to investigate the analgesic effects of low-dose gabapentin administered during the first 24 hours after abdominal hysterectomy.

**Methods.** A prospective, double-blind, randomised study was conducted on 98 patients undergoing abdominal hysterectomy. The patients were divided into two groups: 49 patients received oral gabapentin 400 mg 1 hour before surgery, followed by a further 100 mg 8, 16 and 24 hours after the initial dose, and 49 received placebo. Morphine (5 mg) was used for rescue analgesia. Pain intensity was self-evaluated using a 100 mm visual analogue scale. Data were analysed using SPSS software version 15.0, and the level of significance was set at  $p < 0.05$ .

**Results.** Compared with the placebo group, patients who received gabapentin perceived a significant reduction in postoperative pain in the first hours after hysterectomy (2 hours:  $38.9 \pm 18.1$  v.  $74.9 \pm 15.2$ ,  $p < 0.05$ ; 6 hours:  $37.9 \pm 20.8$  v.  $76.6 \pm 22.4$ ,  $p < 0.05$ ; 12 hours:  $35.8 \pm 24.4$  v.  $79.7 \pm 25.7$ ,  $p < 0.05$ ; 18 hours:  $36.3 \pm 19.1$  v.  $71.7 \pm 20.7$ ,  $p < 0.05$ ; 24 hours:  $40.1 \pm 14.5$  v.  $52.7 \pm 21.1$ ,  $p < 0.05$ ). Opioid requirements 2 hours after surgery were also significantly lower in the gabapentin group than in the placebo group (21 v. 40 patients,  $p < 0.05$ ). No side-effects were reported in either group.

**Conclusions.** Low-dose gabapentin can reduce opioid requirements after abdominal hysterectomy, and increase patient comfort postoperatively.

The management of postoperative pain has received much interest in recent years. The degree of postoperative pain, as ultimately perceived by the patient, is multifactorial and depends on variables such as type and duration of the operation, type of anaesthesia and analgesia used, and the patient's mental and emotional state.<sup>1</sup> If sufficient analgesia is provided, not only will the patient's comfort be increased but the duration of hospital stay will be shortened, reducing both treatment costs and the risk of hospital-acquired infections. Of the many methods of postoperative pain relief, the oldest and most widely used is parenteral opioids.<sup>2</sup>

Although opioid analgesics are the most frequently used drugs for postoperative analgesia, their use is limited by their side-effects.<sup>3</sup> The mechanisms involved in pain suggest that a combination of non-opioid analgesics and opioids might enhance the quality of analgesia and reduce opioid requirements and side-effects.<sup>4</sup> However, non-steroidal anti-inflammatory drugs, which would otherwise be ideal for administration in combination with

opioids, have adverse effects on the gastro-intestinal and haematological systems as well as on renal function.<sup>5</sup>

Gabapentin, a new third-generation anti-epileptic drug, is a structural analogue of gamma-aminobutyric acid (GABA), an important neurotransmitter in the central nervous system.<sup>6</sup> Like other anti-epileptic drugs, gabapentin has been shown to be effective in the treatment of neuropathic and inflammatory pain after surgical operations. Studies in recent years have particularly focused on the efficacy and safety of gabapentin in the treatment of postoperative pain.<sup>7-8</sup>

Gabapentin does not interact with other commonly prescribed drugs. Its most frequent side-effects are somnolence, dizziness and fatigue,<sup>9</sup> which are also common side-effects of widely used premedications. In addition, the side-effects of gabapentin are usually not severe.<sup>10</sup>

Because gabapentin seems to alleviate and prevent acute nociceptive and inflammatory pain and may

reduce postoperative pain, we planned to study its use in patients undergoing elective abdominal hysterectomy for benign conditions. The aim of the study was to determine the effect of low-dose gabapentin in comparison with placebo on postoperative pain and opioid requirements.

## Methods

A prospective, case-controlled, double-blind, randomised study was designed and conducted on 98 women aged between 35 and 55 years and undergoing elective abdominal hysterectomy for benign conditions. All patients were referred to Shahid Sadoughi hospital in Yazd, Iran, between July 2005 and September 2007. The experimental protocol was approved by the hospital research and ethics committee. All the patients were interviewed individually by the researcher, and all provided written informed consent. The exclusion criteria were a known allergy to gabapentin, epilepsy, previous treatment with gabapentin, a chronic pain syndrome, a history of cardiovascular, respiratory, renal or hepatic disease, psychiatric disorders, and substance abuse. Patients who regularly used opioids, or who had used drugs with known analgesic properties within 24 hours before surgery, were also excluded.

Hysterectomies were performed under general anaesthesia, using endotracheal intubation and a standard anaesthetic and analgesic technique.

The sample size selected was based on our hypothesis that gabapentin reduces the need for opioids for postoperative pain treatment. We calculated that we would need 34 patients per group to have an 80% chance of detecting a 35% reduction in 24-hour morphine consumption at a 5% significance level, using a Mann-Whitney test with a 0.05 two-sided significance level (nQuery Advisor, Version 5.0). To enable detection of potential differences in side-effects between the two groups we expected that somewhat larger groups would be required, and 50 patients per group was decided on. However, surgery was postponed in 2 patients and they were excluded from the study.

The patients were randomly allocated to either the gabapentin group (49 patients) or the placebo group (49 patients). Randomisation schedules were prepared using a computer-generated random number table. A nurse from a department not involved in the study prepared the drug-containing bags, each containing four tablets according to the list. The codes of the bags, which allowed the investigators to know which women had received gabapentin and which had been treated by placebo, were disclosed to them only after completion of the statistical analysis of the results.

The patients in the gabapentin group received 600 mg orally 1 hour before surgery, followed by 100 mg 8, 16 and 24 hours after the initial dose, while those in the other group received placebo tablets of similar size and

shape at the same times. One litre of Ringer's lactate was infused intra-operatively and 2 litres during the 12 hours after the operation. After surgery all patients remained in the postoperative care unit for 2 hours. They were closely monitored in the recovery room, where analgesia with intravenous 5 mg morphine was provided on request. Thereafter the patients were transferred to the Department of Gynecology. The standard care for postoperative pain in the Department, based on previous experience, is oral ibuprofen (400 mg) at 4-hour intervals.<sup>11</sup> Patients are informed that they can have a rescue dose of another medication (intramuscular injection of 5 mg morphine) for breakthrough pain if further analgesia is needed before 4 hours elapse.

Pain was self-assessed by the patients on a validated 100 mm visual analogue scale, as instructed by the nursing staff. This pain scale provides a validated and minimally intrusive measure of pain intensity, and ranges from 'No pain' (0) to 'The worst pain imaginable' (100). Patients were instructed to place a mark on the line that indicated the level of pain experienced. The distance in millimeters from the low end of the scale and the patient's mark was used as a numerical index of pain intensity. Questionnaires were filled out for each patient at the beginning of the study and after the operation. During the first 24 hours postoperatively pain intensity was evaluated at 2, 6, 12, 18 and 24 hours, before the administration of each dose of analgesic medication. In our department women are given food orally 6 hours after hysterectomy, are mobilised the morning after the operation, and usually stay in the hospital for 56 - 72 hours. At the end of the observation period the patients were asked to express their opinion concerning the efficacy of the pain-relieving treatment.

Data were analysed using SPSS 15.0 software, with the chi-square test, unpaired *t*-test and Mann-Whitney test, as appropriate;  $p < 0.05$  was considered to be statistically significant.

## Results

Of the 100 patients entered into the study, 2 were excluded because the surgery was postponed, leaving 49 patients in the gabapentin group and 49 in the placebo group. Table I shows that there was no difference in demographic or medical characteristics between the study groups. As a result of the study design, the two study groups were also identical with regard to indications for surgery, type of incision and method of anaesthesia.

Table II presents the postoperative analgesic requirements and pain assessments. Additional analgesia in the postoperative care unit was requested by 40 patients in the placebo group and 21 patients in the gabapentin group ( $p < 0.05$ ). Furthermore, pain assessment in the recovery room and during the first 4 postoperative hours indicated that women in the gabapentin group experienced significantly less pain at the scheduled postoperative pain

**Table I. Demographic characteristics of the study groups**

Characteristic	Gabapentin (N=49)	Placebo (N=49)	p-value
Age (yrs) (mean±SD)	42.4±6.1	43.1±7.9	>0.05
Weight (kg) (mean±SD)	74±10.5	71±12.1	>0.05
Height (cm) (mean±SD)	161±5.4	160±4.7	>0.05
Indication (N (%))			
Myoma	19 (38.8)	20 (40.8)	>0.05
Adenomyosis	9 (18.4)	11 (22.4)	
Abnormal uterine bleeding	21 (42.9)	18 (36.7)	
Operative time (min) (mean±SD)	89±25	91±21	>0.05
Length of hospital stay (h) (mean±SD)	62±7	60±6	>0.05

**Table II. Analgesic requirements in the study groups**

	Gabapentin (N=49)	Placebo (N=49)	p-value
Patient requested opioid in the postoperative care unit (N (%))	21 (42.9)	40 (81.6)	<0.05
Pain scores (mean±SD)			
2 h after surgery	38.9±18.1	74.9±15.2	<0.05
6 h after surgery	37.9±20.8	76.6±22.4	<0.05
12 h after surgery	35.8±24.4	79.7±25.7	<0.05
18 h after surgery	36.3±19.1	71.7±20.7	<0.05
24 h after surgery	40.1±14.5	52.7±21.1	<0.05
Patient requested opioid 24 h after surgery (N (%))	18 (36.7)	31 (63.3)	<0.05
No. of analgesic doses on 1st day (mean±SD)	6±0.0	6±0.0	>0.05
No. of analgesic doses on 2nd day (mean±SD)	2.1±0.9	2.6±0.5	>0.05

measurement intervals, with an average of less than 40 mm on the visual analogue scale. The number of doses of analgesia provided during the first postoperative day was similar, an average of 6 in both groups. Requirements on the second postoperative day were very low, an average of 4 analgesic doses and similar in the two groups.

Table III shows that there were no differences in side-effects between the two groups during the 24-hour postoperative period. About two-thirds of the patients complained of nausea and about one-third had vomiting. Drowsiness was more common in the gabapentin group than in the placebo group, but this was not significant. There was no difference in length of hospital stay or postoperative complications. Women who received gabapentin had higher satisfaction rates than those who received placebo (41 (83.7%) v. 29 (59.2%),  $p < 0.05$ ).

## Discussion

The current study shows that low-dose gabapentin had a significant and beneficial effect on pain perceived

by women during the first 24 hours after abdominal hysterectomy. During this time period, average pain intensities in the gabapentin group were lower than 40 mm, while those in the placebo group were higher than 60 mm. This is of importance, because pain scores of 5 - 44 mm are considered to indicate mild pain and those of 45 - 74 mm moderate pain.<sup>12</sup>

We hypothesise that pain is most severe in the first hours after operation. Recent work suggests that high-dose gabapentin may reduce both postoperative pain intensity<sup>7-8,13</sup> and morphine requirements in the first hours after abdominal hysterectomy.<sup>14</sup> Our findings are similar to those reported previously, but in our study the patients received low-dose gabapentin. Durmus *et al.*<sup>2</sup> compared the effects of a combination of gabapentin and paracetamol with gabapentin alone and placebo on postoperative pain and morphine consumption, and reported that a single dose of gabapentin as well as a combination of gabapentin and paracetamol decreased postoperative opioid requirements and increased patient satisfaction. In contrast, Fassoulaki *et al.*<sup>15</sup> reported

**Table III. Number (%) of patients experiencing side-effects 2 - 24 hours postoperatively**

Side-effect	Gabapentin	Placebo	p-value
Nausea	32 (65.3)	37 (75.5)	>0.05
Vomiting	18 (36.7)	19 (38.8)	>0.05
Drowsiness	26 (53.0)	22 (44.9)	>0.05
Dizziness	5 (10.2)	7 (14.3)	>0.05
Dry mouth	21 (42.9)	24 (49.0)	>0.05
Headache	7 (14.3)	4 (8.2)	>0.05

that gabapentin had no effect on pain and morphine consumption immediately after abdominal hysterectomy but decreased pain 1 month postoperatively. Rorarius *et al.*<sup>13</sup> showed that pre-operative treatment with gabapentin reduced the degree of postoperative nausea and vomiting after vaginal hysterectomy, possibly either because the need for postoperative opioids is reduced or because gabapentin itself has an anti-emetic effect. No differences between the two groups with regard to postoperative nausea and vomiting could be found in the current study, probably because we used low-dose gabapentin. It is likely to be high-dose gabapentin that has anti-emetic effect.

There is still a good deal of controversy regarding pre-operative treatment with gabapentin,<sup>5,7</sup> but these authors investigated other types of surgery.

## Conclusion

Our data suggest that a combination of a single pre-operative dose of gabapentin plus low doses of gabapentin during the first 24 hours postoperatively can reduce pain intensity and opioid requirements and also increases patient satisfaction.

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