

# Evaluation of Pregabalin as an Adjuvant to Patient-controlled Epidural Analgesia during Late Termination of Pregnancy

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## ABSTRACT

**Introduction:** Late termination of pregnancy combines psychological distress with severe physical pain. The present study evaluated the benefit of adding oral pregabalin to epidural analgesia during this procedure.

**Methods:** Healthy women were randomly allocated to receive either oral pregabalin 150 mg/12 h or prazepam 10 mg/12 h at the induction of the late termination of pregnancy procedure. When they felt abdominal pain (numerical rating scale ranging from 0 [no pain] to 100 [worst pain possible]), patient-controlled epidural analgesia was activated and set to deliver ropivacaine 0.1% with sufentanil 0.25  $\mu$ g/ml, 5 ml/h with a bolus dose of 5 ml/30 min. Rescue analgesia was available as needed by administration of 10 ml ropivacaine 0.1% (pain score less than 60/100) or 0.2% (at least 60/100). The primary outcome was the consumption of epidural analgesics.

**Results:** Forty-eight patients participated in the study. Demographic and obstetric data were similar. Pregabalin reduced total ropivacaine consumption  $11.3 \pm 3.2$  mg/h (mean  $\pm$  SD) versus  $15.1 \pm 4.9$  mg/h in the prazepam group ( $P = 0.005$ ), an effect related to a decrease in the need for rescue analgesia. In the pregabalin group, fewer women asked for rescue dose (75 vs. 96%;  $P = 0.048$ ), and the number of rescue doses per patient was reduced (1 [0–2] vs. 2 [1–3]); median [interquartile range],  $P = 0.005$ ), particularly the need for ropivacaine 0.2%.

**Discussion:** This is the first study considering the use of pregabalin for labor pain associated with late termination of

pregnancy, showing that pregabalin 150 mg/12 h is a helpful adjuvant to epidural analgesia. Modulation of both visceral sensitization and affective component of pain may contribute to the benefits observed.

### What We Already Know about This Topic

- ❖ Gabapentin and pregabalin reduce opioid use and pain report after surgery, but their use in labor has not been studied.

### What This Article Tells Us That Is New

- ❖ In 48 women undergoing late termination of pregnancy, pregabalin 150 mg/12 h reduced use of epidural ropivacaine to treat labor pain by 25% and might be a useful adjuvant in this setting.

LATE termination of pregnancy (LTOP) procedures (*i.e.*, medical abortions for severe congenital anomalies or intrauterine death at gestational age greater than or equal to 22–24 weeks) represent only 3% of abortions.<sup>1</sup> Because of its rare occurrence, the management of pain during the procedure has not received a major interest.

Pain experienced in medical abortions causes significant distress whatever the term of the pregnancy.<sup>2</sup> In LTOP, the physical pain due to visceral sensitization from induced labor and cervical ripening is severe and associated with major psychological distress. Epidural analgesia, which is currently the most effective way to manage labor pain, is also effective to alleviate pain during LTOP without interfering with the procedure.<sup>3</sup> However, in the context of LTOP, where any pain is poorly perceived by the parturient, satisfactory pain relief may remain a challenge for the anesthesiologist.<sup>1</sup>

Gabapentin and its analog pregabalin differ structurally and mechanistically from other analgesics. They have been designed as analogs of  $\gamma$ -aminobutyric acid, but their mechanism of action mostly relies on binding to  $\alpha 2$ - $\delta$  subunit of voltage-gated calcium channels in the central nervous system.<sup>4,5</sup> In clinical practice, they have demonstrated effectiveness to relieve epileptic seizures and to treat anxiety disorders. Moreover, they are currently approved for the treatment of neuropathic pain in the United States and in Europe.<sup>4</sup> Pregabalin, the second generation of calcium channel  $\alpha 2$ - $\delta$  ligands, offers the advantages linked to a more reliable phar-

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macokinetic profile with a rapid dose-independent absorption.<sup>6</sup> For a few years now, these drugs have been used as part of multimodal analgesia in the perioperative setting, where they help to reduce postoperative pain and opioids consumption.<sup>7,8</sup> One study has previously demonstrated that gabapentin could potentiate epidural analgesia after orthopedic surgery.<sup>9</sup>

In the literature, several experimental studies have reported the efficacy of gabapentinoids to alleviate visceral pain in animal models.<sup>10–12</sup> Whether pregabalin alleviates pain in patients suffering from irritable bowel syndrome,<sup>13</sup> its efficacy under acute pain conditions (*i.e.*, in patients undergoing minor gynecological procedures) is less evident.<sup>14,15</sup>

To our knowledge, this is the first study applying gabapentinoids in the management of labor pain. The aim was to assess the benefit of using oral pregabalin as an adjuvant to epidural analgesia in the context of LTOP. We hypothesized that oral pregabalin might demonstrate a sparing effect on epidural analgesics consumption. The second aim was to evaluate the analgesic effect of oral pregabalin in a clinical model of visceral pain (*i.e.*, induced labor during LTOP procedure). Because gabapentinoids possess anxiolytic properties, which may have an important role in the context of LTOP, we compared oral pregabalin with an active placebo (*i.e.*, benzodiazepine, an anxiolytic that is commonly used during abortion procedures).

## Materials and Methods

After approval by the Clinical Research Practices Committee (St. Luc Hospital, Brussels, Belgium) and obtaining informed consent, healthy women undergoing LTOP (*i.e.*, medical abortion for severe congenital anomalies or intrauterine death, at gestational age 24 weeks or later) under epidural analgesia were included. Exclusion criteria were patients of American Society of Anesthesiologists classification status of more than 3; patients reporting an intake of anti-convulsants, anxiolytics, and major analgesics; inability to use a patient-controlled epidural analgesia (PCEA) device to rate pain; and patients with contraindications to regional analgesia. Just before induction of the standardized procedure, lumbar epidural puncture was performed with an 18-gauge Tuohy needle, and an epidural catheter was inserted 4 cm at the L3–L4 level in all parturients. All the catheters were placed by an attending physician in anesthesiology or under the direct supervision of an attending physician. The insertion of the catheter was immediately followed by administration of a 3-ml lidocaine-epinephrine 1:200,000 test dose and by a single epidural bolus dose of 10 ml ropivacaine 0.1%. That bolus dose was used to ensure the correct position of the epidural catheter (a bilateral level of at least T10 was assessed by ether test) and to permit the performance of a feticide if planned.

The women were then randomly allocated to receive either oral pregabalin 150 mg/12 h or oral prazepam 10 mg/12 h (an active placebo) until delivery. Pregabalin was chosen

according to a more favorable pharmacokinetic profile, allowing a more reliable use than gabapentin.<sup>6</sup> The decision to administer a dose of 150 mg was made because of the lack of effect previously reported when using a pregabalin dose of either 75<sup>15</sup> or 100 mg<sup>14</sup> for gynecological procedures.

Before the beginning of the study, according to a computer-generated randomization, 48 identical envelopes including 2 capsules of either pregabalin 150 mg (Lyrica® Pfizer Ltd., Sandwich, Kent, United Kingdom) or prazepam 10 mg (Lysanxia®; Pfizer Inc., Brussels, Belgium) had been numbered and sealed. The capsules were prepared by the pharmacy to maintain double-blind conditions. Each patient who agreed to participate in the study received one envelope given by the midwife in charge of the case and was told to take one capsule every 12 h. The first oral intake of either pregabalin or prazepam began at the induction of the LTOP procedure (*i.e.*, at the time of intravaginal administration of misoprostol according to the standardized protocol established by the obstetricians).

The patients were also instructed in the use of the numerical rating scale (NRS; 0 [no pain] to 100 [worst pain]) to rate their pain and on how to use the PCEA device. They were told to request the epidural analgesia as soon as they felt abdominal pain. When the women requested the activation of epidural analgesia, they were connected to a PCEA device delivering ropivacaine 0.1% with sufentanil 0.25 µg/ml, set as a continuous infusion of 5 ml/h with a bolus dose of 5 ml/30 min. In the case of pain occurring under epidural analgesia, the patients were told to first self-administer a PCEA bolus dose. If the pain was not relieved within the next 15 min, rescue analgesia was available by administration of bolus doses of 10 ml ropivacaine 0.1% (NRS less than 60/100) or 10 ml ropivacaine 0.2% (NRS is at least 60/100).

The duration of the LTOP procedure was the time from the first administration of intravaginal misoprostol until delivery. The following parameters were recorded for the utilization of the PCEA: the duration of PCEA use (time from PCEA activation until delivery), the time elapsed between the induction of LTOP procedure associated with the intake of the first pregabalin or prazepam tablet and the request for PCEA activation as well as the NRS pain score at that time, the number of PCEA bolus doses administered, and the hourly consumption of ropivacaine self-administered by the patient using the PCEA. Concerning rescue analgesia, the following parameters were noticed: the number of rescue doses requested during the LTOP procedure (excluding the first epidural dose directly after the test dose), the total dose of ropivacaine needed (rescue doses were administered according to the pain scores expressed by the patients as aforementioned), the time elapsed between the beginning of LTOP procedure and the first rescue dose, the cervical dilatation at the first rescue dose, and the maximal NRS pain score recorded during the requests of rescue doses. Finally, the total consumption of epidural ropivacaine during the procedure was calculated taking into account both PCEA use and rescue doses. The adverse effects (*i.e.*, excessive sedation,

headaches, dizziness, and visual disturbance) in relation with the intake of pregabalin and prazepam were monitored during the procedure and also recorded after delivery. Side effects such as nausea, vomiting, and diarrhea were not taken into account because their occurrence is commonly observed after misoprostol administration.<sup>16</sup>

In the particular context of LTOP, to respect as much as possible the privacy of the patients, pain scores were only assessed when a rescue analgesic dose was requested. Further, we did not ask the patients to fill out validated questionnaires evaluating their level of anxiety.

### Statistical Analysis

Results were expressed as mean  $\pm$  SD, confidence interval, or median (interquartile range), as indicated. According to a Kolmogorov-Smirnov normality test, parametric data between the groups were compared by unpaired Student *t* test and nonparametric data by Mann-Whitney Rank Sum test; a *P* value less than 0.05 was considered to be significant (SigmaStat 3.5; Systat Software GmbH, Erkrath, Germany). Categorical data were compared using chi-square test and Fisher exact test using a two-tailed probability.

The primary outcome was the total consumption of epidural ropivacaine during the procedure. A retrospective analysis conducted on a previous set of 10 pilot patients reported a mean consumption of  $16 \pm 5.5$  mg/h of ropivacaine during LTOP procedure. We calculated that 21 patients per group were needed to demonstrate a ropivacaine sparing effect of 30% with a power of 0.8 at an  $\alpha$  level of 0.05. A second outcome of the study was the effect of pregabalin on visceral pain. The retrospective data showed an average NRS pain score of  $52 \pm 19$  at the activation of PCEA. We calculated that 23 patients per group were needed to demonstrate a 30% reduction of pain after pregabalin intake, with a power of 0.8 at an  $\alpha$  level of 0.05. Consequently, we decided to include 24 patients per group (*i.e.*, a total of 48 patients in the study).

### Results

All patients completed the study. Demographic and obstetric data were similar between the prazepam group and the pregabalin group (table 1). The average duration of the LTOP procedure, from intravaginal misoprostol until delivery, was  $15 \pm 6$  h. The average duration of epidural analgesia (PCEA use) was  $10 \pm 5$  h. Although time elapsed between the induction of the LTOP procedure (and therefore the intake of the first dose of either pregabalin or prazepam) and the patient's request for the activation of epidural analgesia did not differ, NRS pain scores assessed at that time were significantly higher in the prazepam group (table 2).

The administration of oral pregabalin improved epidural analgesia better than a regular benzodiazepine and allowed a significant reduction of the hourly consumption of ropivacaine (fig. 1). The difference observed between the groups was not linked to a different use of the PCEA technique

**Table 1.** Demographic Data

Parameters	Group Prazepam (n = 24)	Group Pregabalin (n = 24)
Age, yr	31 $\pm$ 6	31 $\pm$ 5
Weight, kg	66 $\pm$ 9	67 $\pm$ 8
Height, cm	164 $\pm$ 8	166 $\pm$ 6
Previous pregnancies, n	2 (1–3)	2 (1–3)
Previous deliveries, n	0 (0–1)	1 (0–2)
Primiparas, n	11	10
Gestational age, weeks	26.5 (24–31)*	28 (24–34)*
Feticide, n	12	14
Fetus weight, g	1,456 $\pm$ 1,055	1,357 $\pm$ 833
LTOP duration, min	942 $\pm$ 421	829 $\pm$ 358

Values are mean  $\pm$  SD or median (interquartile range) unless otherwise indicated. No significant statistical differences between the two groups. Duration of LTOP (late termination of pregnancy) procedure was the time elapsed between the beginning of the procedure (*i.e.*, intravaginal misoprostol) and fetus delivery.

\* Median (extreme values).

(number of PCEA bolus doses was similar) but rather accounted for a clinically significant reduction of the needs for rescue analgesia (table 2). Fewer patients needed the administration of rescue doses in the pregabalin group (75 *vs.* 96%, *P* = 0.048). Further, the number of rescue doses per patient was lower in the pregabalin group as well as the total dose of ropivacaine administered during the external interventions of the anesthesiologist, according to the pain score expressed by the patient (table 2). The differences were specifically observed for the needs of ropivacaine 0.2%, which was administered in case of severe pain (NRS  $\geq$  60/100). At least one epidural dose of ropivacaine 0.2% was necessary in 20 patients (83%) in the prazepam group *versus* 13 patients (54%) in the pregabalin group (*P* = 0.05). Patients in the prazepam group received 2 (1–2) rescue doses of ropivacaine 0.2% during the procedure by comparison with 1 (0–1) dose in the pregabalin group (*P* = 0.03).

Retained placenta occurred in three patients of the prazepam group and in four patients of the pregabalin group. Very few adverse effects occurred in relation with pregabalin and prazepam intake; only one patient in pregabalin group reported blurred vision (disappearing within the 12 h). No patient complained of excessive sedation, vertigo, or dizziness.

### Discussion

To our knowledge, this is the first study to evaluate the benefit of gabapentinoids under acute pain conditions in relation to the management of induced labor. Our results go along with those of Turan *et al.*<sup>9</sup> who reported the benefit of gabapentin as an adjuvant to epidural analgesia combining bupivacaine and fentanyl for postoperative pain management. We found that oral pregabalin 150 mg/12 h is a useful adjuvant to epidural analgesia in women undergoing LTOP, allowing a reduction of 27% in epidural analgesics consump-

**Table 2.** Analgesia during the Procedure

	Group Prazepam (n = 24)	Group Pregabalin (n = 24)	P Value
PCEA duration, min	677 ± 375	615 ± 318	0.562
Time before PCEA activation, min	260 (115–408.5)	189 (121–300)	0.299
NRS score (0–100) at PCEA activation	54 ± 15	32 ± 14	<0.001
PCEA bolus doses, n	7.9 ± 4.7 (95% CI: 6–10)	6.6 ± 2.7 (95% CI: 5–8)	0.267
Rescue analgesia			
Patients who needed, n	23	18	0.048
Rescue doses, n	2 (1–3)	1 (0–2)	0.005
Ropivacaine dose (mg)*	40 (20–51.5)	20 (20–30)	0.034
Time before first rescue dose, min	300 (170–621)	330 (180–509)	0.962
Cervical dilatation at first rescue dose, cm	2 (1.5–6)	6.5 (3–9)	0.05
Maximal NRS score (0–100) during rescue doses	72.5 ± 15	63 ± 11	0.05

Values are mean ± SD (95% CI) or median (interquartile range). Duration of PCEA use was the time elapsed between patient's request to use epidural analgesia and fetus delivery. Treatment groups were Prazepam (oral administration of prazepam 10 mg/12 h) and Pregabalin (oral administration of pregabalin 150 mg/12 h).

\* Rescue doses were administered according to NRS pain score as follows: 10 ml ropivacaine 0.1% at NRS less than 60/100 or 10 ml ropivacaine 0.2% at NRS greater than or equal to 60/100.

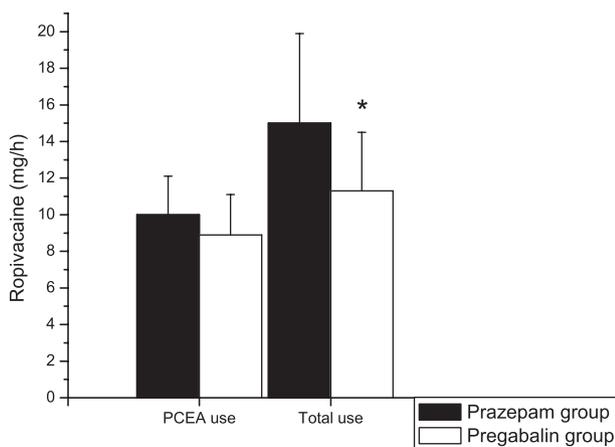
CI = confidence interval; NRS = numerical rating scale; PCEA = patient-controlled epidural analgesia.

tion. In the context of LTOP, the use of pregabalin decreased significantly the needs for rescue analgesia, thereby reducing the workload of caregivers and certainly contributing to the privacy of the patients. The discrepancy between the greater effect observed by Turan *et al.*<sup>9</sup>, who demonstrated a 40% sparing effect in PCEA requirements, and our findings may result not only from different drugs and doses used but more certainly from different pathophysiological conditions. In effect, the Turan *et al.*<sup>9</sup> study involved postoperative pain intensity, which decreases with time, whereas pain intensity in LTOP increases with the progression of the labor. Furthermore, the pain conditions in Turan *et al.*<sup>9</sup> concerned

somatic pain from orthopedic procedures, whereas LTOP and labor pain are almost exclusively of visceral origin.

According to our findings, although pregabalin administration did not have a direct effect on the use of PCEA (no difference in the number of PCEA bolus self-administered), epidural analgesia seemed more effective in the pregabalin group, in which patients requested fewer external interventions for rescue analgesia, particularly to treat severe pain. Several explanations may account for the effect of pregabalin in the present context of LTOP: reduced visceral pain and sensitization process, greater potentiation of epidural analgesics, and modulation of the affective component of pain related to a greater decrease of anxiety.

Although some clinical trials have previously questioned the benefit of pregabalin to alleviate visceral pain after gynecological procedures,<sup>14</sup> our findings seem to argue for an effective modulation of visceral pain by pregabalin during induced labor for LTOP. In effect, pregabalin decreased by 40% the NRS pain scores assessed before PCEA activation and allowed a clinically significant reduction of the number of rescue doses, specifically the need for using ropivacaine 0.2%, which was administered in case of severe pain (NRS ≥60/100). Compounds such as gabapentin and pregabalin bind to the auxiliary  $\alpha 2\text{-}\delta$  protein subunit of voltage-gated calcium channels, at both spinal and supraspinal levels, and thereby modulate neuronal activity by reducing the influx of calcium and the subsequent release of neurotransmitters.<sup>4,5</sup> However, it is noteworthy that  $\alpha 2\text{-}\delta$  ligands have minimal effect on physiologic transmitter release but significantly inhibit sensitized or abnormal release. In other words, pregabalin will have greater effectiveness in pathologic conditions associated with peripheral and central sensitization, as demonstrated with inflammatory and neuropathic pain. The cervical ripening process used to induce labor (*i.e.*, the administration of prostaglandin misoprostol) provokes the



**Fig. 1.** Ropivacaine consumption (milligrams per hour): patient-controlled epidural analgesia (PCEA) including continuous infusion and autoadministered bolus doses; total use including PCEA use and additional rescue doses needed during the late termination of pregnancy procedure. \*  $P = 0.005$  between the groups. Groups of treatment: oral administration of prazepam 10 mg/12 h (group Prazepam) and oral administration of pregabalin 150 mg/12 h (group Pregabalin).

synthesis and the release of inflammatory products and causes severe abdominal pain requiring analgesia in more than 60% of the women.<sup>16,17</sup> LTOP usually necessitates repeated prostaglandin administration throughout the procedure, which may result in low abdomen sensitization and visceral hyperalgesia. One can hypothesize that such underlying conditions have contributed to pregabalin effectiveness in contrast with a previous study that reported no benefit of oral pregabalin after minor gynecological surgery but that had excluded patients requiring preoperative misoprostol for cervical ripening.<sup>14</sup> Besides pain arising from cervical ripening, visceral pain during LTOP also involves pain from uterine contractions inducing spinal sensitization. Human studies have demonstrated increased cerebrospinal fluid concentrations of excitatory amino acids, such as aspartate and glutamate, in women experiencing visceral pain during labor.<sup>18,19</sup> According to an experimental model of visceral nociception, the analgesic effect of gabapentin is associated with the modulation of the spinal excitatory neurotransmitters.<sup>10</sup> Finally, pregabalin was particularly effective to reduce the needs for rescue analgesia, particularly during the episodes of intense abdominal pain. Transient worsening of pain, also called breakthrough pain, either spontaneous or provoked, is observed not only in cancer patients but also in various acute pain conditions, including postoperative pain.<sup>20</sup> Central sensitization is supposed to play a major role in the causes of such episodes.

Besides the modulation of visceral pain, an interaction with epidural analgesics and specifically the opioid derivative may account for the benefit of pregabalin, as demonstrated in human volunteers<sup>21</sup> as well as in experimental models of acute visceral pain.<sup>12</sup> Moreover, in acute pain conditions, gabapentinoids act at a supraspinal level to activate the inhibitory descending noradrenergic system.<sup>22</sup> The analgesic synergy between spinal adrenergic agonists and spinal opioids is well established.

Finally, the neuropsychotropic effects of pregabalin might have contributed to the modulation of the affective component of the pain (*i.e.*, the suffering) and thereby allowed the reduction of the physical pain experienced during LTOP. Benzodiazepines are frequently used in abortions, although their effectiveness to modulate anxiety and pain is questioned.<sup>23</sup> In the context of day-case surgery, pregabalin (75–300 mg) increases perioperative sedation in a dose-related manner but fails to reduce state anxiety<sup>15,24</sup>. These results raise the question of whether pregabalin might have an anxiolytic effect within the first hours after a single-dose administration by contrast with the efficacy demonstrated during long-term treatment of generalized anxiety disorder.<sup>4,5</sup> Nutt *et al.*<sup>25</sup> have found that a preoperative dose of pregabalin 150 mg provided a clinically meaningful anxiolytic effect within 4 h of intake, although the speed of response was not as rapid as it was after administration of alprazolam, an active placebo. The difference among the aforementioned studies relies on the fact that Nutt *et al.*<sup>25</sup> have evaluated patients' anxiety for several hours after pre-

gabalin intake, whereas in the negative studies,<sup>15,24</sup> the authors have assessed anxiety state only at 1 h after pregabalin administration. Consequently, they could have missed an anxiolytic effect of the drug that might have been beneficial in our patients.

In conclusion, oral pregabalin 150 mg/12 h is an effective adjuvant to epidural analgesia combining local anesthetic and lipophilic opioid during induced labor for LTOP, a distressful procedure combining severe visceral pain and psychological suffering. At the dose used, it is well tolerated and more effective than benzodiazepine. Pregabalin intake allows reduced epidural consumption, particularly by decreasing the needs for external interventions to provide rescue analgesia. Several mechanisms may contribute to the beneficial effect in this context, which includes a modulation of visceral pain and central sensitization, a potentiation of epidural analgesia, and a modulation of the affective component of the pain.

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