

The effects of preoperative oral pregabalin and perioperative intravenous lidocaine infusion on postoperative morphine requirement in patients undergoing laparotomy

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OBJECTIVES: To evaluate and compare the effects of preoperative oral pregabalin and perioperative intravenous lidocaine infusion on postoperative morphine requirement, adverse effects, patients' satisfaction, mobilization, time to first defecation and time to discharge in patients undergoing laparotomy.

METHODS: Eighty patients (18 to 65 years of age) undergoing elective laparotomy were randomly divided into four groups (n=20 in each group): group C, placebo capsules and normal saline infusion perioperatively (control); group L, placebo capsules and lidocaine 1 mg/kg intravenous bolus dose followed by 2 mg/kg/h infusion until skin closure; group P, 150 mg oral pregabalin and normal saline infusion perioperatively; and group PL, 150 mg oral pregabalin and lidocaine 2 mg/kg/h infusion until skin closure. Hemodynamic parameters, visual analogue scale (VAS) scores, analgesic consumption, side effects, time to mobilization, time to first defecation, time to discharge and patients' satisfaction were recorded.

RESULTS: VAS scores of group L, group P and group PL were lower than group C (P<0.05). Morphine consumption of group P and group PL was lower than group C (P<0.05). Incidence of nausea in group C was higher than group L and group PL. Time to first defecation and mobilization were shorter in group L and group PL compared with group C (P<0.05).

CONCLUSION: Preoperative oral pregabalin and perioperative intravenous lidocaine infusion decreased postoperative VAS scores. Preoperative oral pregabalin decreased morphine requirement and perioperative intravenous lidocaine infusion hastened gastrointestinal motility and mobilization, and decreased the incidence of nausea in patients undergoing laparotomy. Therefore, preoperative pregabalin with or without lidocaine provides superior pain relief in patients undergoing laparotomy.

Key Words: Laparotomy; Lidocaine; Postoperative pain; Pregabalin

Les effets de la prégabaline préopératoire par voie orale et de la perfusion intraveineuse de lidocaïne périopératoire sur les besoins postopératoires en morphine des patients qui subissent une laparotomie

OBJECTIFS : Évaluer et comparer les effets de la prégabaline préopératoire par voie orale et de la perfusion intraveineuse périopératoire de lidocaïne sur les besoins postopératoires en morphine, les réactions indésirables, la satisfaction des patients, la mobilisation, le délai jusqu'à la première défécation et le délai jusqu'au congé chez les patients qui subissent une laparotomie.

MÉTHODOLOGIE : Quatre-vingts patients (de 18 à 65 ans) qui subissaient une laparotomie non urgente ont été répartis au hasard en quatre groupes (n=20 dans chaque groupe). Le groupe C recevait des capsules placebo et une perfusion de soluté physiologique (sujets témoins); le groupe L, des capsules placebo et un bolus intraveineux de 1 mg/kg de lidocaïne suivi d'une perfusion de 2 mg/kg/h jusqu'à la guérison de la plaie; le groupe P, 150 mg de prégabaline par voie orale et une perfusion périopératoire de soluté physiologique; et le groupe PL, 150 mg de prégabaline par voie orale et une perfusion de 2 mg/kg/h de lidocaïne jusqu'à la guérison de la plaie. Les chercheurs ont consigné les paramètres hémodynamiques, les scores de l'échelle analogique visuelle (ÉAV), la consommation d'analgésiques, les réactions indésirables, le délai jusqu'à la mobilisation, le délai jusqu'à la première défécation, le délai jusqu'au congé et la satisfaction des patients.

RÉSULTATS : Les scores de l'ÉAV des groupes L, P et PL étaient plus faibles que ceux du groupe C (P<0,05). La consommation de morphine par les groupes P et PL était plus faible que celle du groupe C (P<0,05). L'incidence de nausées dans le groupe C était plus élevée que dans les groupes L et PL. Le délai jusqu'à la première défécation et la mobilisation étaient plus courts dans les groupes L et PL que dans le groupe C (P<0,05).

CONCLUSION : La prégabaline préopératoire par voie orale et la perfusion intraveineuse périopératoire de lidocaïne réduisaient les scores postopératoires de l'ÉAV. La prégabaline préopératoire par voie orale réduisait les besoins en morphine, tandis que la perfusion intraveineuse périopératoire de lidocaïne accélérait la motilité gastro-intestinale et la mobilisation et réduisait l'incidence de nausées chez les patients qui subissaient une laparotomie. Ainsi, la prégabaline préopératoire avec ou sans lidocaïne assure un soulagement supérieur de la douleur chez les patients qui subissent une laparotomie.

dose of opioids by combining drugs and methods with different modes of action (5).

Pain after surgery has a neuropathic component as well as somatic and visceral characteristics, and agents that are effective in the treatment of neuropathic pain are effective in reducing central sensitization (6). Pregabalin is a gamma-aminobutyric acid analogue with anti-convulsant effect. Although the primary indication is neuropathic pain, recent studies have evaluated the efficacy of pregabalin in the treatment of acute postoperative pain (7,8).

Despite improvements in technology and pharmacology, adequate management of postoperative pain in patients undergoing major surgery remains challenging and more than 50% of patients continue to experience moderate to severe pain (1-3). Although regional analgesia techniques provide intense pain relief, they may result in rare but potentially devastating complications (4). Opioid-related side effects may delay recovery and rehabilitation. Recent studies have focused on the concept of 'multimodal analgesia' to achieve optimal analgesia, and to reduce the side effects and the required

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TABLE 1
Patient characteristics and duration of surgery

Characteristic	Groups			
	Control	Pregabalin	Lidocaine	Pregabalin + lidocaine
Age, years	53.2±15.7	54.0±23.8	51.1±26.2	51.7±19.1
Body weight, kg	70.0±16.7	69.7±28.7	72.2±25.5	74±25.2
Sex, male/female, n/n	10/10	8/12	11/9	8/12
Duration of surgery, min	101.0±78.0	113.3±93.6	114.1±89.8	99.6±145.6

Data presented as mean ± SD unless otherwise specified. $P > 0.05$ among groups

TABLE 2
Perioperative mean arterial pressure (mm Hg) and heart rate (beats/min)

Time	Control		Pregabalin		Lidocaine		Pregabalin + lidocaine	
	Blood pressure	Heart rate	Blood pressure	Heart rate	Blood pressure	Heart rate	Blood pressure	Heart rate
0 min	104.3±40.5	92.2±36.2	104.6±31.6	86.3±28.0	104.5±28.4	91.2±27.0	96.2±35.1	87.4±33.3
15 min	103.3±41.3	92.4±27.2	96.0±52.5	84.9±30.6*	91.9±28.8	86.1±27.4*	90.8±42.3	81.5±29.9*
30 min	96.5±47.8	92.3±24.2	89.7±35.9	85.4±27.9*	87.2±35.0	85.7±29.8*	92.0±37.4	84.1±29.4*
60 min	94.6±31.3	89.6±25.8	89.1±48.1	82.1±26.3	91.8±36.2	74±21.6	86.1±30.4	78.8±24.9
90 min	87.6±40.2	83.4±15.8	87.5±39.4	80.4±34.9	91.1±31.5	74.1±9.2	84.7±22.0	75.7±27.1
120 min	85.6±25.4	78.4±25.6	81.7±32.7	74.2±22.7	96.7±33.1*	73.8±29.2	73.2±73.2*	71.5±31.7
150 min	75.2±23.4	72.4±14.2	84.2±36.3	74±12.3	88.0±24.8	73.7±31.4	77.5±18.9	74±45.1

Data presented as mean ± SD. * $P < 0.05$ versus control

Lidocaine is a local anesthetic agent that produces an analgesic effect by modifying response to neurons in the dorsal horn, and an anti-inflammatory effect by inhibiting migration and metabolic activation of leukocytes (8). Lidocaine has a positive effect on the return of gastrointestinal motility, which has been attributed to earlier mobilization (9-11).

The aim of our study was to investigate the effects of preoperative oral pregabalin and perioperative intravenous lidocaine infusion in patients undergoing laparotomy on postoperative morphine consumption, adverse effects, gastrointestinal motility, patient satisfaction, time to mobilization and time to discharge.

METHODS

After the approval of the Central Ethics Committee of Pharmaceutical General Directorate of the Ministry of Health (No: 1713 / Date: September 30, 2010) and patients' written consent, the present prospective, randomized, placebo-controlled and double-blinded study included a total of 80 patients, American Society of Anesthesiology classification I to II, 18 to 65 years of age and undergoing elective laparotomy between November 2010 and April 2011. Patients for whom informed consent was not obtained, had American Society of Anesthesiology scores \geq III, liver or kidney failure, chronic pain, epilepsy or other neurological disease or a history of allergy to one of the study drugs were excluded from the study.

The patients were randomly divided into four groups (n=20 per group). In group C (control-placebo), patients ingested placebo capsules 12 h before the operation and on the morning of the operation, and received saline infusion perioperatively. Group L (lidocaine) patients ingested placebo capsules 12 h before surgery and on the morning of surgery, and received a bolus injection of 1.0 mg/kg lidocaine at induction of anesthesia, then a continuous infusion with a Braun Perfusor infusion pump (B. Braun Melsungen, Germany) at a rate of 2 mg/kg/h during the operation until skin closure. Group P (pregabalin) patients ingested 150 mg pregabalin 12 h before surgery and on the morning of surgery, and received saline infusion perioperatively. Group PL (pregabalin + lidocaine) patients ingested 150 mg pregabalin 12 h before surgery and on the morning of surgery, and received bolus injection of 1.0 mg/kg lidocaine at induction of anesthesia, then a continuous infusion at a rate of 2 mg/kg/h perioperatively until skin closure. Randomization was performed with sealed envelope method before the day of surgery when patients arrived to the ward reception area.

Anesthesia was induced with 5 mg/kg to 7 mg/kg thiopental sodium and 0.1 mg/kg intravenous vecuronium bromide in all patients

and was maintained with 1 MAC desflurane and 70% nitrogen dioxide in oxygen. Perioperative heart rate, arterial blood pressure, peripheral oxygen saturation and end-tidal carbon dioxide pressure monitoring were performed and the data were recorded at 30 min intervals. Postoperatively, intravenous morphine was administered until visual analogue scale (VAS) scores were < 30 , and intravenous patient-controlled analgesia (PCA) consisting of 1 mg/mL morphine solution with 1.5 mg bolus dose and 8 min lockout interval was started in the recovery room.

Postoperative VAS scores (at rest, with coughing and with movement) were first measured in the postanesthesia care unit (time point 0). The measurements were recorded at 2 h intervals for the first 8 h, 4 h intervals for the second 8 h and continued at 6 h intervals for 48 h. Measurements included mean arterial pressure, heart rate, respiratory rate, PCA consumption, additional analgesic requirement, side effects, time to mobilization, time to first defecation and time to discharge. Patient satisfaction scores using a four-point Likert scale questionnaire (0 = poor, 3 = excellent) were recorded in all patients.

Intraoperatively, measurement of mean arterial pressure and heart rate began following placement of hemodynamic monitors and were measured at 15 min intervals.

Statistical analysis

To demonstrate a 30% difference in postoperative morphine requirement, it was estimated that 19 patients per group would be required for $\alpha = 0.05$, $\beta = 0.1$ (power 90%) with a standard effect size of 1.18. The data obtained were compared statistically using repeated-measures ANOVA and the post hoc Tukey-Kramer test; nonparametric data were evaluated using the Kruskal-Wallis test. $P < 0.05$ was considered to be statistically significant.

RESULTS

There was no significant difference among groups in terms of the demographic characteristics and the duration of surgery ($P > 0.05$, Table 1). No statistical difference was found among the groups with respect to perioperative mean arterial pressure ($P > 0.05$, Table 2). Perioperative heart rate at 15 min, 30 min and 60 min was significantly lower in group P, group L and group PL compared with group C ($P < 0.05$, Table 2).

No difference was detected among the groups with regard to morphine loading dose in the recovery room ($P > 0.05$). VAS scores were found to be statistically lower in group P, group L and group PL than in group C between 2 h and 16 h postoperatively ($P < 0.05$, Table 3).

TABLE 3
Postoperative pain rating using visual analogue scale scores (0 mm to 100 mm)

Time	Control	Pregabalin	Lidocaine	Pregabalin + lidocaine
0 h	67.0±8.8	60.9±10.5	59.8±10.0	59.1±9.7
2 h	44.2±7.6	35.9±9.7*	42.5±9.6*	38.8±9.1*
4 h	42.3±8.9	31.9±8.8*	34.2±10.0*	33.0±7.8*
6 h	39.8±6.5	27.9±5.2*	33.3±8.4*	28.8±5.8*
8 h	34.0±7.2	24.0±5.3*	31.0±8.9*	29.1±5.2*
12 h	32.3±6.6	23.4±5.7*	29.3±5.2	28.8±6.3*
16 h	29.0±7.0	24.0±5.7*	28.2±6.7	26.3±4.2*
22 h	25.0±7.4	23.7±4.9	24.7±4.8	25.3±4.5
28 h	27.2±5.8	24.3±5.7	27.1±9.4	23.4±6.5
34 h	25.4±4.1	25.5±7.0	23.9±3.3	22.7±4.6
40 h	24.8±5.8	24.2±3.0	22.6±2.9	22.9±5.0
48 h	23.1±4.2	22.05±2.9	21.25±4.1	19.5±5.1

Data presented as mean ± SD. *P<0.05 versus control

Total PCA morphine consumption was lower in the first postoperative 4 h interval in group P (mean [± SD] 16.9±13.1 mg) and group PL (16.4±17.5 mg) compared with the control group (24.2±16.4 mg) (P<0.05). Morphine consumption was also significantly lower after the postoperative 34 h interval in group P (53.5±49.1 mg) and group PL (65.9±72.8 mg) compared with the control group (87.1±49.3 mg) (P<0.05). Compared with group C, morphine consumption was statistically lower in group P only at the 40 h (58.6±53.6 mg versus 93.2±52.9 mg) and 48 h (62.8±55.4 mg versus 99.7±54.7 mg) intervals (P<0.05).

There was no difference among groups with respect to return of bowel sounds. Time to first defecation and mobilization times were statistically shorter in group L and group PL compared with group C (P<0.05, Table 4).

There was no significant difference among groups in terms of itching. The incidence of nausea was lower in group L and group PL (two of 18 and five of 15 patients experienced nausea, respectively, P<0.05). Seven patients in group P and 13 patients in group C had nausea (Table 5).

There was no significant difference among groups in terms of patient satisfaction.

DISCUSSION

In the present study, it was found that preoperative oral pregabalin reduced postoperative VAS scores and morphine requirements, while perioperative intravenous lidocaine infusion had a positive effect on VAS scores, gastrointestinal functions, mobilization time and decreased the incidence of nausea. Pregabalin with or without lidocaine provided superior pain relief in patients undergoing laparotomy.

Postoperative pain may have adverse effects on the respiratory, cardiovascular, endocrine, immune, gastrointestinal and locomotor systems, particularly after major surgical procedures, as well as disrupting patient comfort, increasing morbidity and even mortality (1). Postoperative pain has a neuropathic component, which may be perceived as hyperalgesia, hyperesthesia or hypoesthesia as a result of peripheral and central sensitization. The incidence of acute postoperative neuropathic pain has been reported to be 1% to 3% in 2002 (12).

Administration of systemic opioid and nonsteroidal anti-inflammatory drugs, or injection of neuraxial or perineural local anesthetic and opioid combinations are the most frequently used methods for postoperative pain treatment. However, these methods are inadequate for many patients. Therefore, anticonvulsant agents such as gabapentin and pregabalin, which are effective in the treatment of chronic neuropathic pain, have been used in the treatment of acute postoperative pain in recent years (2,13,14).

Doses of gabapentin and pregabalin for treatment of postoperative pain ranged from 300 mg to 1200 mg and 150 mg to 300 mg, respectively (14,15). Pregabalin was chosen for the present study because it is

TABLE 4
Time to first bowel sound, defecation, mobilization and discharge, h

Variable	Control	Pregabalin	Lidocaine	Pregabalin + lidocaine
Bowel sound	22.9±6.1	22.0±3.5	24.8±3.5	24.4±3.6
Defecation	40.8±10.0	38.6±6.1	32.9±5.5*	34.5±5.3*
Mobilization	19.2±3.0	18.3±2.8	17.3±2.4*	17.1±2.8*
Discharge	104.4±27.0	98.5±10.6	97.7±12.5	92.3±9.7

Data presented as mean ± SD. *P<0.05 versus control

TABLE 5
Postoperative side effects

Side effect	Control	Pregabalin	Lidocaine	Pregabalin + lidocaine
Pruritus (yes/no)	4/16	0/20	1/19	1/19
Nausea (yes/no)	13/7	7/13	2/18*	5/15*

*P<0.05 between groups

easier to use in acute pain due to its linear pharmacokinetics (16). As in our study, it has been observed that gabapentin and pregabalin decreased postoperative opiate requirements (17,18).

In patients undergoing laparoscopic gastrectomy, a single preoperative dose of 150 mg pregabalin decreased VAS values and morphine consumption during the first 24 h postoperatively (19). Paech et al (20) administered a preoperative dose of pregabalin 100 mg and intraoperative acetaminophen in patients undergoing minor gynecological surgery and reported that postoperative pain scores and the fentanyl consumption were similar to the placebo group. This study was performed in ambulatory patients, and side effects and analgesic requirements were interrogated later by telephone. Early discharge also reduced the use of parenteral analgesics.

Systemic local anesthetics have been used for acute and chronic pain for many years. The preferred intravenous anesthetic is lidocaine because of rapid onset and intermediate duration of action (21). Although there are a number of studies concerning the effects of pregabalin and lidocaine on postoperative pain, mobilization, time to discharge and postoperative gastrointestinal system functions, ours is the first study comparing the effects of the combination of two medications with each alone and with placebo. We used two 150 mg doses of pregabalin (12 h and 45 min before surgery). In most studies, pregabalin was administered 1 h to 2 h before surgery as a single dose (22,23). In a study investigating the effects of perioperative infusion of lidocaine on major abdominal surgery (20), patients were administered a 1.5 mg/kg loading dose 30 min before surgical incision followed by 1.5 mg/kg/h infusion until the end of the first postoperative hour; the total dose of morphine administered by PCA and the additional morphine requirements were found to be lower than those of control group.

The effect of systemic lidocaine on discharge of patients undergoing colorectal surgery was examined and it was reported that bowel function started earlier with lidocaine and that patients were discharged earlier (11). Groudine et al (24) found similar results in patients undergoing radical retropubic prostatectomy. In the two studies, infusion of lidocaine continued until the end of the first postoperative hour. We stopped lidocaine infusion after closure of skin incision and found the mean time to defecation was shorter. In the two studies related to the postoperative lidocaine infusion, no analgesic effect could be observed (11,25). It was believed that lidocaine infusion, to be effective, should be given during nociceptive stimulus (26). Lidocaine was also found to be as effective as epidural block on postoperative pain, bowel functions and hospital discharge in patients undergoing colonic resection (27).

The occurrence and the incidence of side effects is important for the quality of postoperative analgesia. Pregabalin has negligible interaction with other drugs and is well tolerated. Adverse effects such as somnolence, dizziness, confusion, headache, ataxia and weight gain

have been reported (28-31). While many of these side effects are due to chronic use of pregabalin, the most common side effects in postoperative patients are dizziness, somnolence and sedation. We did not detect any statistically significant difference in pruritus. Schulmeyer et al (19) reported a significant reduction in nausea, vomiting and the use of antiemetics in patients undergoing laparoscopic gastrectomy with preoperative 150 mg pregabalin. Preoperative pregabalin 150 mg did not increase the incidence of side effects in patients undergoing laparoscopic cholecystectomy. However, Mathiesen et al (30) administered pregabalin 300 mg and pregabalin 300 mg plus dexamethasone 8 mg to patients undergoing arthroscopy under spinal anesthesia and found that significantly increased sedation and nausea occurred in the pregabalin only group compared with pregabalin plus dexamethasone group and controls. The antiemetic effect of dexamethasone may contribute to this result. More adverse effects such as drowsiness, blurred vision and difficulty in walking were reported in patients given pregabalin 600 mg (31). It has been shown that the higher the dose used, the more analgesic

effect as well as the higher incidence of adverse effects are observed. To balance the analgesic effect and side effects, we consider that using two doses of 150 mg may be more appropriate. High-dose lidocaine has been reported to have side effects such as paresthesia, nystagmus, convulsion and arrhythmia; however, we did not observe any of these effects.

CONCLUSION

Preoperative oral pregabalin decreased VAS scores. Intraoperative lidocaine infusion decreased the incidence of nausea and hastened the return of gastrointestinal motility. We conclude that preoperative pregabalin with or without lidocaine reduced morphine requirements and provided superior pain relief compared with placebo in patients undergoing laparotomy.

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