Research Article

Pregabalin for Postoperative Analgesia after Idiopathic Scoliosis Surgery

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Abstract

Introduction: Postoperative pain management in children after spinal surgery is a crucial issue that deserves much attention. Multimodal analgesia appears to be the most appropriate approach to optimize pain control. Pregabalin has proven its efficacy in improving postoperative pain scores and considerably reducing opioid consumption in adults. The aim of the study was to demonstrate the analgesic effect of pregabalin for postoperative pain relief after scoliosis surgery in adolescents.

Methods: Forty adolescents with idiopathic scoliosis scheduled to undergo a posterior corrective spinal surgery, were assigned to receive either pregabalin 150 mg orally (pregabalin group, n=20) or a placebo (control group, n=20) one hour before surgery and 12 hours postoperatively. Patient received also, paracetamol 15 mg/Kg four times per day, 20 mg of piroxicam orally twice-a-day and morphine administered via PCA pump, for 48 hours. Total postoperative morphine consumption and severity of pain at rest and on movement using a 10 cm-Visual analogic scale pain score were measured 48 hours following surgery.

Results: Total 48-hour PCA morphine consumption was significantly lower in the pregabalin group than in the control group [mean (SD) 29.8 mg (13.2) vs. 43.1 mg (20.7), P=0.014]. However, there were no differences between groups in the median VAS pain scores at rest and on movement. No significant differences were found with regard to side effects in the initial 48 hours after surgery.

Conclusions: A per operative total dose of 300 mg oral pregabalin in adolescents undergoing surgical correction of idiopathic scoliosis, was associated with a significant reduction in 48-h morphine consumption.

ABBREVIATIONS

PCA: Patient Controlled Analgesia; TCI: Target-Controlled Infusions; VAS: Visual Analogic Scale; ASA: American Society of Anesthesiology - Physical Status

INTRODUCTION

Posterior spinal fusion as a surgical correction of idiopathic scoliosis in children is a major spinal surgery well known for being source of severe and prolonged pain that can persist up to 3 days. Thus, appropriate postoperative pain control is required to allow early mobilization and improve functional recovery. Although opioids are considered to be the cornerstone of postoperative pain management, they are frequently associated with nausea, vomiting, urinary retention, pruritus or excessive sedation [1]. The more recent concept of multimodal analgesia is now the standard of care, since it has demonstrated its superiority in pain relief, while reducing opioid-related adverse effects. Postoperative pain following spinal surgery comes from the various bending and rotational forces applied to the vertebrae with instrumentation, as well as the extensive surgical damage made to bones and muscles which generally stimulate both peripheral and central pain pathways. This may result in excessive and prolonged nociceptive sensitization of dorsal horn neurons, causing, if maintained, allodynia and hyperalgesia.

Gabapentin and, more recently, pregabalin are structural analogs of γ-aminobutyric acid (GABA) featuring interesting antiallodynic and antihyperalgesic properties that may be effective in controlling neuropathic pain [2,3]. They also prevent central sensitization development, which can be rather beneficial in acute postsurgical pain management, as part of multimodal analgesia regimen. Furthermore, pregabalin demonstrates predictable and linear pharmacokinetics, making it easy to use in clinical practice [4]. Besides, it has proven, over the last years, its efficacy in improving postoperative pain scores and considerably reducing both opioid consumption and related side effects in different surgical settings [5-8].

Until now, only gabapentin has been assessed in children undergoing scoliosis surgery in two trials with contrasting results [9,10]. Although pregabalin is still prescribed off-label in children population, recent studies results suggested that it can be safely used at a certain dose as an antiepileptic drug in refractory childhood epilepsy [11,12]. Pregabalin has also dramatically reduced chemotherapy-induced neuropathy pain in paediatric oncological patients [13].

We hypothesized that pregabalin, as an adjunct to multimodal analgesia after scoliosis surgery in children, may reveal the opioid-consumption sparing effect that has already been shown with gabapentin.

MATERIALS AND METHODS

After Local Research Ethics committee approval, written informed consent was obtained at preoperative visits from both adolescents and parents for this clinical prospective, randomized, double-blind, placebo-controlled trial. The study was conducted on 40 patients of either gender, between March 2010 and March 2013.

Inclusion criteria were adolescents (belonging to the 14 to 18 age group, weighing at least 40 Kg) with idiopathic scoliosis scheduled to undergo a posterior corrective spinal surgery, ASA physical status III or less, and ability to follow instructions on how to operate a Patient-controlled Analgesia (PCA) pump.

Patients were excluded if they were unable to cooperate, had history of gastric ulcer, seizure or any severe concomitant disease (neuromuscular scoliosis, neurodegenerative disease), contraindications or known allergy to any of the medications used in the study, a history of alcohol or drug abuse, patients who were taking pregabalin or sustained-release opioids for other medical purposes, morbid obesity (body mass index > 40 Kg/m^2), and patients scheduled for anterior spinal fusion or spinal reoperation.

All patients were operated by only two surgeons. They had a posterior Cotrel Debousset instrumentation in prone position without intraoperative traction. None of patients had osteotomy. We use awake test for intraoperative global neurological evaluation.

According to a computer-generated random allocation, patients were assigned to 2 treatment groups to receive either pregabalin (Lyrica® - Pfizer, USA) 150 mg orally (pregabalin group, n=20) or a placebo (control group, n=20) one hour before surgery and 12 hours postoperatively. The schedule was under the responsibility of our hospital investigational pharmacy, which was otherwise neither involved in clinical care of patients, nor in the present study conduct.

In the operating room, all patients were monitored with continuous electrocardiogram, noninvasive blood pressure, pulse oximetry, capnography and temperature.

Anesthetic technique was standardized. Both groups received oral midazolam (0.5 mg/Kg, maximum 10 mg) (Midazolam 2m.ml - Medis, Tunisia) as a premedication. Anesthesia was induced and maintained with target-controlled infusions (TCI) of propofol (Propofol Freisinius 20 mg.ml) (using the Schneider pharmacokinetic model) and remifentanil (Remifentanil 5 mg – Medis) (using the Minto model) with the objective to maintain perioperative MAP at 65 mmHg. Tracheal intubation was facilitated and perioperative muscle relaxation was obtained with cisatracurium (Cistract 5 mg.ml - Medis) 0.15 mg/Kg followed by 0.05 mg/Kg as clinically indicated. The lungs were mechanically ventilated with a mixture of oxygen in air (FiO$_2$ 0.5) maintaining normocapnia (end-tidal carbon dioxide partial pressure 4.7-5.3 kPa). At the time of skin closure, analgesia was anticipated with paracetamol 15 mg/Kg and morphine 0.1 mg/Kg intravenously. Subsequently, TCI was stopped and residual neuromuscular blockade was reversed with neostigmine 40 mcg/Kg and atropine 20 mcg/Kg. All patients received ondansetron (Andosetron 4 mg – Medis) 0.1 mg/Kg (max 4 mg) as an anti-emetic medication. A dose of 1.5 g cefuroxime was employed as antibiotic prophylaxis, administered 30 min during anesthesia induction and continued for the next 24 hours (2 additional doses of 750 mg). Tranexamic acid at a dose of 10 mg/kg was continuously infused for 30 minutes prior to wood incision and continued at a dose of 10mg/kg/h until the end of surgery.

After tracheal extubation and assessment of lower limbs motor function, patients were transferred to the postanesthesia recovery unit where they were given paracetamol 15 mg/Kg four times per day, 20 mg of piroxicam (Piroxen 20 mg - Medis) orally twice-a-day and morphine administered via PCA pump (1mg dose, 7 minutes lockout, and a total cumulative dose not exceeding 7.5 mg hourly). For early rehabilitation, patients were sited on day2 and walked on day 3 or 4.

The severity of postoperative pain at rest and on movement (raising bed up to 45°) was measured using a 10-cm VAS (with 0 cm corresponding to absence of pain, and 10 cm to worst pain imaginable) at 1, 2, 4, 6, 12, 24, 36 and 48 hours following surgery. Hemodynamics (systolic and diastolic blood pressure, cardiac frequency), oxygen saturation and respiratory rate were also observed at the same measurement time points. Side effects (nausea, vomiting, pruritus, urinary retention, constipation...) were recorded and treated. Sedation was measured using a three-point sedation scale (3= spontaneously awake without stimulus, 2= drowsy but easily arouses to consciousness, 1= arouses slowly to consciousness with sustained painful stimulus, 0= unresponsive to painful stimulus). All Patients were sited on day2 and walked on day 3. Demographic data (age, gender, weight, length, ASA physical status, operating time, number of vertebral levels, intra operative bleeding) was collected preoperatively and during operative period. Total postoperative morphine consumption was recorded on the PCA device at 48 hours.

The primary outcome of our study was to evaluate the analgesic efficacy of pregabalin in postoperative pain management in adolescents undergoing posterior spinal fusion, by comparing 48-h total morphine consumption. The secondary outcomes were: 10 cm-VAS pain score at rest and on movement, incidence of postoperative nausea and vomiting, headache, sedation, respiratory depression and urinary retention.

Statistical analysis

Sample size estimation was based on previous adult studies using morphine consumption as a primary outcome following spinal fusion surgery. Assuming a study power of 0.80, accepting a two-tailed *α level of 0.05 and using a power analysis of t student testing on 2 independent means, a total of 19 patients would be required to show a reduction of 14 mg in morphine consumption. So we enrolled 20 patients in each group, to account for dropouts.*

Statistical analyses were performed with SPSS statistical software (SPSS, Chicago, IL, USA) version 20. Descriptive statistics were included to examine sample and between-group characteristics. The distribution of data was checked by the

Kolmogorov-Smirnov test. Categorical data were examined with Pearson's chi-square test or Fisher's exact test and presented as number (%). Parametric data were analyzed using independent sample Student's t-test and presented as mean (standard deviation). Nonparametric data were analyzed using Mann-Whitney U-test and presented as median (interquartile range). P values less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Forty-four patients with idiopathic scoliosis scheduled for posterior spinal fusion were assessed for eligibility. Forty were enrolled in the study and all of them were able to complete it. No differences were identified between the pregabalin and placebo groups for all demographic data and operative period details (Table 1). Postoperative hemodynamic and respiratory parameters did not differ among the two treatment groups at any measurement time point. Total 48-hour PCA morphine consumption was significantly lower in the pregabalin group than in the control group [mean (SD) 29.8 mg (13.2) vs. 43.1 mg (20.7), P=0.014 (Figure. 1)]. However, there were no differences between groups in the median VAS pain scores at rest and on movement (Figures 2,3). No significant differences were found with regard to opioid-related side effects in the initial 48 hours after surgery. Mild nausea was reported in 5 patients in the pregabalin group (25%) and 7 patients in the control group (35%). One patient in both groups (5%) complained from itching. There was no significant difference between groups in the level of sedation (Table 2). We didn't report any surgical complication during hospital stay (7 to 10 days).

DISCUSSION

Postoperative pain management in children after idiopathic spinal fusion surgery is a crucial issue that deserves much
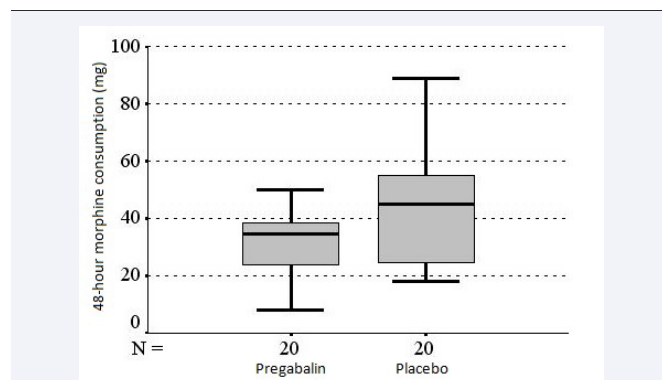
Figure 1 Box and whisker plot of total 48-hour morphine consumption. Values are expressed as mean and SD. Significant difference between groups (P=0.014).
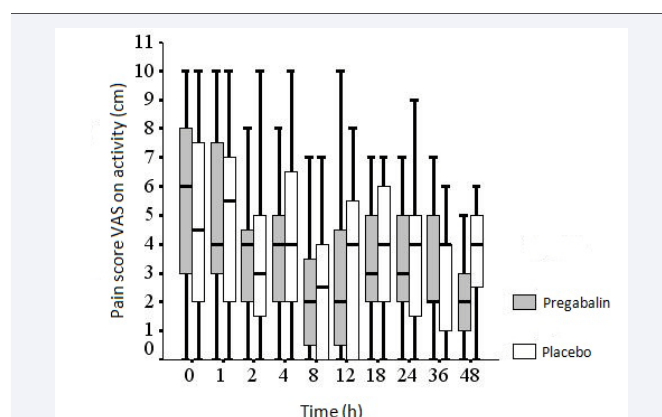
Figure 2 Box and whisker plot of VAS pain score on movement of pregabalin group (grey boxes) and control group (white boxes) over time. The line in the middle of the box represents the median value, the ends of the boxes represent the interquartile range and whiskers represent the minimum and maximum values. No significant difference between groups.
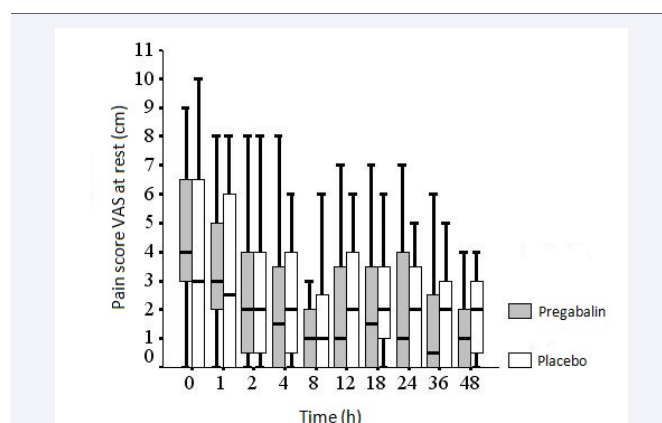
Figure 3 Box and whisker plot of VAS pain score at rest of pregabalin group (grey boxes) and control group (white boxes) over time. The line in the middle of the box represents the median value, the ends of the boxes represent the interquartile range and whiskers represent the minimum and maximum values. No significant difference between groups.

Table 1: Baseline data of patients recruited.

	Pregabalin group (n=20)	Control group (n=20)	p
Age (years)	17.1 (2.6)	16.5 (1.8)	0.48
BMI (kg/m^2)	19.2 (3.1)	20.8 (2.7)	0.09
Cobb angle (°)	62.4 (7.8)	65.1 (8.0)	0.43
Duration of surgery (h)	5.2 (0.6)	5.1 (0.8)	0.53
Number of vertebral levels	12 (1)	12 (2)	0.51
Operative blood loss (ml)	1360.5 (434.2)	1322.7 (489.2)	0.79

Table 2: Side effects in pregabalin and control groups over 48 h. Data are numbers (%).

	Pregabalin group (n=20)	Control group (n=20)
Nausea	5 (25)	7 (35)
Vomiting	3 (15)	4 (20)
Pruritus	1 (5)	1 (5)
Urinary retention	1 (5)	0 (0)
Sedation (level 2)	10 (50)	8 (40)

attention. Resorting to multimodal analgesia appears to be the most appropriate approach to optimize pain control in this situation.

Recent advances in the pathophysiology of pain have suggested that gabapentinoids proceed by selectively binding to the $\alpha2\delta$ subunit of the presynaptic voltage-dependent calcium channels, which are up regulated in the dorsal root ganglia and spinal cord, and inhibiting calcium influx *via* these channels, thereby generating antinociception.

Recently, pregabalin has been demonstrated to be an effective adjunct to multimodal analgesia in several reviews and meta-analyses by not only reducing opioid consumption [6] but also decreasing the incidence and intensity of both acute [14] and chronic postsurgical pain [15]. Besides, it has been assessed in various surgical settings including major spinal surgery in adults where it has been shown to reduce both opioid consumption and early postsurgical pain [16-18]. Pregabalin was also associated with less pain intensity and improved functional outcomes 3 months after spinal surgery [18-20]. In a recent systematic review, Preoperative use of pregabalin was efficacious in reduction of postoperative pain, total morphine consumption, and incidence of nausea after spine surgery in adult [21].

Regarding spinal surgery for scoliosis in children, only two studies examined the analgesic efficacy of perioperative gabapentin, with contrasting results [9,10].

Rusy et al. [9], found that a preoperative initial load of gabapentin 15 mg/Kg followed by a continued use for 5 days did reduce the amount of morphine consumed and decreased pain scores in the first 48 hours. On the other side, Mayell et al. [10], did not show any significant difference in opioid consumption or pain scores following a single preoperative dose of gabapentin 600 mg. The outcomes variance may be related to a dosage difference. Indeed, Rusy et al., used approximately 825 mg gabapentin preoperatively with a positive impact on their results [9], whereas only 600 mg gabapentin were used in Mayell study, which may explain their negative findings [10].

Pregabalin, meanwhile, was evaluated only in adult patients undergoing spinal surgery [17-19]. Thus, the trial we conducted was the first pediatric-sample based study to assess the analgesic efficacy of pregabalin after major spinal surgery.

In this trial, we have administered 15 0mg of pregabalin 60 minutes prior to surgery, followed by 150 mg 12 hours postoperatively, and evaluated its effects on morphine consumption, pain scores and opioid side effects over 48 hours, in the pediatric spinal fusion.

Our results demonstrate the effectiveness of a 300 mg pregabalin total dose, used as an adjunct to multimodal analgesia, in reducing morphine consumption significantly in the early postoperative period [29.8 mg (13.2) vs. 43.1 mg (20.7), *P*=0.014]. We found no differences in VAS pain scores at rest and on movement between the two groups. We postulate that this was related to the use of PCA morphine device allowing patients to have self-administered boluses when experiencing pain. Moreover, our study was underpowered to demonstrate

differences in pain scores, albeit these results were consistent with literature data as many authors reported that pregabalin administration did not reduce pain intensity for the first 24 hours postoperatively [6]. Furthermore, pain was often in the moderate to severe range in our study (3 < VAS < 6), especially during the first postoperative hours. This may be due to poor initial understanding of the PCA pump operation.

A total dose of 300 mg pregabalin is the most commonly adopted dosing regimen in studies evaluating this medication for spinal surgery in adult patients. It is considered to be the minimal effective dosage in treating both postoperative acute pain [8,19,22] and chronic neuropathic pain [8,16]. In the recent meta analysis [21], results indicated that a high dose of pregabalin (≥300mg/ d) reduced significantly the VAS score with rest at 12hours, 24hours, and 48hours with a significant. But, both high doses and low doses of pregabalin (<300mg/d) reduced the cumulative morphine at 48 hours. Our choice of 300 mg (which approximately corresponds to 6 mg/Kg) was based on safety studies in adults [23,24] while taking into consideration the maximal allowed pregabalin doses used in pediatrics to control refractory childhood epilepsy [11]. Furthermore, it appears that using pregabalin at doses that can reach 10mg/kg/day, which are anticipated to result in similar exposure to the approved adult dose of 600 mg/day, would display acceptable safety and be generally well tolerated by children aged 1 month to 16 years with refractory partial seizures [12].

Pregabalin use is commonly associated with less opioid-related side effects [5,6,8]. In our study, there was no significant difference between groups in such side effects, although we assumed their incidence would be lower in the pregabalin group since they required less morphine during the postoperative period. Regarding pregabalin in itself, its most reported adverse effects are related to central nervous system and include somnolence, dizziness and behavioral change [23]. Preoperative pregabalin administration (75 to 300 mg) usually increase incidence of sedation in a dose-dependent fashion, which results in higher sedation scores whenever pregabalin is used at a 300 mg dosage [6,24]. In our study, patients included in the pregabalin group did not show higher sedation levels.

Our study had some limitations, such as the exclusion of neurogenic scoliosis patients with high opioid-related respiratory risk, knowing that they could have taken advantage from a preoperative pregabalin load too. Another limitation was that we did not evaluate the long-term effects of pregabalin on the incidence of chronic pain following spinal fusion in children. This would be an interesting topic for future work.

CONCLUSION

In conclusion, a perioperative total dose of 300 mg oral pregabalin in adolescents with idiopathic scoliosis undergoing surgical correction was associated with a significant reduction in 48-h morphine consumption while not increasing the incidence of side effects. These findings warrant further studies at a larger scale, which should begin to explore other dosing regimen of pregabalin in pediatric spinal fusion in order to establish analgesic consensus, and even consider the inclusion of neurogenic scoliosis patients.

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