Gabapentin as Premedication for Postoperative Analgesia in Children: A Prospective Randomized Controlled Study

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Abstract

Background: In recent studies, preoperative administration of gabapentin appears to play a role in postoperative pain control. However its use in children is still need further researches. So we aimed to evaluate the effect of gabapentin on management of postoperative orthopedic pediatric pain and consumption of analgesia.

Patients and methods: This prospective study was carried out within one year on 80 children patients aged 10-12 years old scheduled for orthopedic surgery in upper and lower limbs. Patients were randomly allocated equally in two groups (40 for each) as follows: Group I: Gabapentin 300 mg was given orally 2 h before induction of anesthesia (Gabapentin capsule). Group II: control group (receive placebo 2 h before induction of anesthesia).

Results: There was a significant increase in values of pain score at 0.5 h, 4 h postoperative as (P<0.05) as compared in group II with group I, but there was no statistically significant difference in values of pain score at 1 h, 2 h, 6 h, 12 h, 24 h postoperative as (P>0.05) between both groups. There was a significance increase in values of heart rate at 0.5, 4 h postoperatively (P<0.05) as compared group II with group I, but there was no statistically significant difference in values of heart rate at pre-induction and at 1 h, 2 h, 6 h, 12 h, 24 h postoperative as (P>0.05) between both groups. There was a significant increase in values of mean arterial pressure at 0.5, 4 h postoperatively as compared group II with group I and there was no statistically significant difference in values of mean arterial pressure at pre-induction and at 1 h, 2 h, 6 h, 12 h, 24 h postoperative as (P>0.05). There was a significant increase in values of postoperative total analgesia consumption in group II (control group) when compared to group I (gabapentin group) as (P<0.05). There was a significance increase in time to first demand of analgesia in group I when compared to group II (P<0.05).

Conclusion: Administration of gabapentin preoperatively significantly reduces postoperative pain and postoperative analgesia consumption in children under going orthopedic surgery. It also causes stability in hemodynamic status by decreasing stress response and anxiety.

Keywords: Gabapentin; Premedication; Analgesia; Children

Introduction

Severe postoperative pain is a widespread problem in pediatric. Many patients still suffer from moderate to severe postoperative pain despite day improvements in pain treatment [1]. Severe pain leads to reduction of patient satisfaction, late postoperative ambulation, the development of chronic postoperative pain, increased incidence of pulmonary and cardiac complications and increase morbidity and mortality. Therefore, it is of great importance to use optimal analgesic control in surgical procedures that are associated with severe pain [2] effective pain control is provided by opiates but their use is associated with a high incidence of nausea and vomiting, respiratory depression and sedation [3]. Other widely used methods include non-steroidal anti-inflammatory drug, infiltration of local anesthetics or blocking nerves. Gabapentin is an antiepileptic drug that has been extensively used to treat painful neuropathies as diabetic polyneuropathy, post herpetic neuralgia, and neuropathic pain in general [4]. Gabapentin may produce antinociception by binding to presynaptic voltage-gated calcium channels thus inhibiting calcium influx via these channels, and subsequently inhibiting the release of excitatory neurotransmitters (e.g., substance P, calcitonin gene-related peptide) from the primary afferent nerve fibers in the pain pathway, it decreases the hyperexcitability of dorsal horn neurons induced by tissue injury. Central sensitization of these neurons leads to chronic neuropathic pain after trauma and surgery [5]. Acute postoperative pain can be reduced by an antihyperalgesic drug like gabapentin. Gabapentin may also prevent opioid tolerance and has anxiolytic properties [6].

Aim of the Work

The aim of this study is to evaluate the effect of gabapentin on management of postoperative pediatric pain and consumption of analgesia.

Patients and Methods

After approval of Tanta Faculty of Medicine Ethics Committee, this prospective study was carried out between October 2014 and October 2015. Eighty children, aged 10-12 years, ASA physical status I or II scheduled for orthopedic surgery ( Which were managed by open reduction and internal fixation) were included in the study. Written informed consent was obtained from parents of each child included in the study.
Patients undergoing orthopedic surgery with age between 10 and 12 years and parents able to give informed consent were included in this study.

Patients with diabetes, liver and/or kidney disease, hypersensitivity to drugs used, swallowing disorder, epilepsy or previous treatment with gabapentin or opioids analgesia were excluded from this study.

Patients were randomly allocated equally in two groups (40 for each) as follows: Group I, Gabapentin 300 mg was given orally 2 h before induction of anesthesia (Gabapentin capsule) while Group II: control group (received placebo 2 h before induction of anesthesia). The randomization was performed using sealed numbered envelopes indicating the group of each patient. A blind nurse who did not participate in patients’ follow up read the number and made group assignments.

A blinded chief nurse who did not participate in data collection confirmed that each patient ingested the medications as was scheduled. The process of inclusion in the study went on until the required number of patients was reached.

Preoperative investigations including CBC, kidney function, liver function, PT, and INR.

After admitting the patients to the surgery room, 22 G intravenous cannula was placed and their heart rate, noninvasive blood pressure and arterial oxygen saturation was monitored. All the patients received 1 μg/kg fentanyl anesthesia was inducted using propofol 2 mg/kg, and 0.5 mg/kg atracurium was used to facilitate endotracheal intubation. Anesthesia was continued using a mixture of oxygen and air with the ratio of 50% and isoflurane. After extubation and ensuring adequate respiration, the patients were transferred to the recovery room for 30 min; then, they were transferred to the ward.

Postoperative pain intensity was measured by visual analog scale (0 being the absence of pain and 10 the maximum level of pain). Pain intensity will be rated as mild (VAS between 0-3), moderate (VAS between 4-6), and severe (VAS between 7-10) (at 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h and 24 h after the surgery [7]. Vital sign as heart rate, mean arterial blood pressure were measured at 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h and 24 h after the surgery. First time for requesting analgesia was recorded, if VAS ≥ 4 the patient will receive i.v. 15 mg/kg paracetamol and 10 mg meperidine with minimal interval 4 h between the consecutive doses. Total analgesic consumption within 24 h was recorded.

**Sample size**

The sample size was calculated using Epi-Info software statistical package created by World Health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The sample size was calculated at N=30

The criteria used for sample size calculation were as follows:
- 95% confidence limit
- 80% power
- The ratio between experimental and control groups is 1:1
- Expected outcome in in treatment group is double times better than control groups. (40-80% of optimal required)

**Statistical analyses**

Statistical presentation and analysis of the present study was conducted, using the mean, standard Deviation, Student t-test [Unpaired], paired t-test and chi-square tests by SPSS V. 20.

**Chi-square**

The hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chisquare and likelihood-ratio chi-square. Fisher’s exact test and Yates’ corrected chi-square are computed for 2 x 2 tables.

Significant level: Non Significant>0.05 Significant<0.05* High Significant<0.001*

**Results**

This prospective study was carried out within one year on 80 children patients aged 10-12 years old scheduled for orthopedic operation in upper and lower limbs.

There was no statistically significance difference in demographic data between both groups (P>0.05), so both groups are comparable (Table 1).

| Weight (kg) | Duration(min) | Sex |
|------------|---------------|-----|
| **Group I** | **Group II** | **Group I** | **Group II** |
| Range      | 20.0 - 35.0   | 18.0 - 36.0 | 90 - 120 | 90 - 120 |
| Mean ± SD  | 26.53 ± 4.40  | 26.80 ± 6.65 | 105.35 ± 9.11 | 105.37 ± 8.92 |
| T-test     | 0.074         | 0.483         | χ²          | 0.208      |
| P-value    | 0.941         | 0.63          | P-value     | 0.648      |

**Table 1:** Comparison between both groups according to sex, weight and duration of surgery.

As regards to the (VAS) recordings: In group I The values of pain score were ranged from 0-3, 1-5, 1-5, 1-5, 2-5, 2-6 and 2-6 with a mean value of 1.28 ± 0.88, 2.63 ± 1.23, 2.63 ± 1.25, 2.25 ± 0.67, 3.10 ± 1.78, 3.50 ± 1.34, and 3.95 ± 1.22 at 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h, 24 h postoperative respectively, while in group II, the values of pain score were ranged from 3-6, 1-6, 1-5, 1-5, 1-5, 1-5, 1-5 and 3-6 with a mean value of 4.05 ± 0.93, 2.43 ± 1.34, 2.73 ± 0.95, 3.73 ± 1.28, 3.75 ± 1.06, 3.8 ± 1.1 and 4.08 ± 1.14 at 0.5 h, 1 h, 2 h, 4 h, 12 h, 24 h postoperative respectively.

In comparison of values of pain score between both groups:

There was a significant increase in values of pain score at 0.5, 4 h postoperative as (P<0.05) as compared in group II with group I, but there was no statistically significant difference in values of pain score at 1 h, 2 h, 6 h, 12 h, 24 h postoperative as (P>0.05) between both groups (Table 2).
Heart rate (HR) recordings (beat/min): In group I The values of heart rate were ranged from 78-96, 79-87, 82-93, 81-93, 81-88, 85-92, 83-94 and 85-94 with a mean value of 87.23 ± 3.91, 87.70 ± 2.04, 86.58 ± 3.21, 86.53 ± 3.36, 85.58 ± 1.82, 88.00 ± 2.05, 85.55 ± 3.57 and 89.91 ± 2.98 at pre-induction and at 0.5 h, 1 h, 2 h, 4 h, 12 h, 24 h postoperative respectively.

In comparison of values of heart rate in group I between pre-induction and 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h and 24 h postoperative was found to be significant in increase in values of heart rate between pre-induction and 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h and 24 h postoperative respectively (P<0.05). While in group II the values of heart rate were ranged from 82-94, 85-94, 83-94, 83-93, 82-93, 82-94, 84-94 and 85-94 with a mean value of 85.90 ± 3.35, 89.83 ± 2.79, 87.18 ± 2.65, 89.53 ± 3.31, 87.48 ± 2.77, 85.33 ± 3.27, 89.18 ± 2.64 and 87.23 ± 2.68 at pre-induction and at 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h, and 24 h postoperative respectively. There was a significant increase in values of heart rate between pre-induction and 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h, 24 h postoperative respectively (P<0.05) and in comparison of values of heart rate between both groups: There was a significance increase in values of heart rate between pre-induction and 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h and 24 h postoperatively as (P<0.05) and there was no significance increase in values of heart rate between pre-induction and 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h and 24 h postoperatively as (P>0.05). While in group II the values of heart rate were ranged from 82-94, 85-94, 83-94, 83-93, 82-93, 82-94 and 85-94 with a mean value of 85.90 ± 3.35, 89.83 ± 2.79, 87.18 ± 2.65, 89.53 ± 3.31, 87.48 ± 2.77, 85.33 ± 3.27, 89.18 ± 2.64 and 87.23 ± 2.68 at pre-induction and at 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h, and 24 h postoperative respectively. There was a significant increase in values of heart rate between pre-induction and 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h, 24 h postoperative respectively (P<0.05) and in comparison of values of heart rate between both groups: There was a significance increase in values of heart rate between pre-induction and 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h and 24 h postoperatively as (P<0.05) and there was no significance increase in values of heart rate between pre-induction and 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h and 24 h postoperatively as (P>0.05).
While in comparison of value of mean arterial pressure between both groups: There was a significant increase in values of mean arterial pressure at 0.5 h, 4 h postoperative as compared group II with group I and there was no statistically significant difference in values of mean arterial pressure at pre-induction and at 1 h, 2 h, 6 h, 12,24 h postoperative as (P>0.05) (Table 4).

| Groups | Group I | Group II | T-test | P-value |
|--------|---------|----------|--------|---------|
| Preinduction | 82.33 ± 3.53 | 83.33 ± 3.29 | 1.311 | 0.194 |
| 0.5 h | 83.75 ± 3.45 | 86.13 ± 3.95 | 2.863 | 0.005* |
| 1 h | 84.43 ± 3.41 | 85.4 ± 2.64 | 1.43 | 0.157 |
| 2 h | 83.83 ± 3.21 | 84.25 ± 2.66 | 0.645 | 0.521 |
| 4 h | 85.08 ± 3.48 | 83.35 ± 2.15 | 2.664 | 0.009* |
| 6 h | 84.45 ± 3.13 | 83.63 ± 2.12 | 1.38 | 0.171 |
| 12 h | 83.33 ± 2.22 | 83.78 ± 2.2 | 0.91 | 0.366 |
| 24 h | 82.63 ± 1.55 | 82.73 ± 1.47 | 0.297 | 0.768 |

**Table 4**: Comparison between postoperative MAP (mmhg) recordings in both groups.

As regards to the rescue analgesia: In group I (Gabapentin group) the total postoperative consumption of meperidine and paracetamol (mg) in group I was ranged from 0-30, 0-1500 (mg) with a mean value of 17.43 ± 7.51, 691.03 ± 320.75 respectively, while in group II (control group) the total postoperative consumption of meperidine and paracetamol in group II was ranged from 10-40, 400-2200 (mg) with a mean value of 30.50 ± 7.49, 1215 ± 382.3 respectively. In comparison between both groups in total analgesia consumption: There was a significant increase in values of postoperative total analgesia consumption in group II (control group) when compared to group I (Gabapentin group) as (P<0.05) (Table 5). The First time demand of analgesia in group I the values of first time demand of analgesia were ranged from 1-24 h postoperatively with a mean value of 6.56 ± 8.41. While in group II the values of first time demand of analgesia were ranged from 0.5 h-4 h postoperatively with a mean value of 0.9 ± 0.74.

In comparison between both groups in first time demand of analgesia: There was a significance increase in time to first demand of analgesia in group I when compared to group II (P<0.05) (Table 5).

| Groups | Group I | Group II | T-test | P-value |
|--------|---------|----------|--------|---------|
| Pre and 0.5 h | 0.004* | <0.001* |
| Pre and 1 h | 0.002* | <0.001* |
| Pre and 2 h | 0.024* | 0.153 |
| Pre and 4 h | <0.001* | 0.964 |
| Pre and 6 h | <0.001* | 0.591 |
| Pre and 12 h | 0.1 | 0.392 |
| Pre and 24 h | 0.59 | 0.226 |

**Table 5**: Rescue Analgesia: meperidine and paracetamol consumption in both groups.

There was no statistically significant difference in postoperative adverse effects between both groups (P>0.05) as regarding nausea, vomiting, headache, dizziness, ataxia and somnolence (Table 6).

**Table 6**: Postoperative adverse effects.

Discussion

Control of postoperative pain is very important postoperative duty, According to the type of surgery, different methods have been used to control the pain. Tissue injury causes alldynia and hyperalgesia due to activation of both the peripheral and central pain pathways [8].

Tissue damage and inflammatory changes release of chemical mediators, which stimulate nociceptors to fire at a lower threshold [9]. Management of postoperative pain is important for children to minimize acute physiological and behavioral distress that leads to improvement the outcomes [10]. Anticonvulsant, such as gabapentin, suppress spontaneous neuronal firing and have beneficial effect in treating chronic, centrally mediated neuropathic pain syndromes[11].
this study, we aimed to evaluate effect of gabapentin in management of postoperative orthopedic pediatric pain and consumption of analgesia. Eighty children ASA I and II included in this study scheduled for orthopedic surgery under general anesthesia aged between 10-12 years.

In this study we found that there was a significant decrease in values of visual analogue score in gabapentin group compared to control group and analgesia consumption was less in gabapentin group than control group.

Giulianne et al. made a study on Twenty female dogs, aged 6 to 12 years undergoing elective mastectomy. The dogs were randomly assigned to one of the two groups, with 10 animals in each. The dogs were orally (PO) administered with either 10 mg/kg (1ml/5kg) of gabapentin solution (Neurontin Oral solution, 10mg/ml, Pfizer, New York, NY, U.S.A.) (Gabapentin, n=10) or 1 ml/5 kg of placebo solution (Placebo, n=10) 120 min prior to surgery. The postoperative gabapentin or placebo was continued for three days after surgery. Pain was assessed using a Visual Analogue Scale (VAS, 0-100 mm) where, 0=no pain and 100=worst possible pain, manifested by vocalization, mastectomy reduced with gabapentin [12]. In consistence to this study, aggression and refusal to allow examination and found that the controlled trial was done by Ahmad et al. on 90 patients aged (10-25) years undergoing elective mastectomy which agreed with the result of this study [13]. Although, Anju et al. made a study on Twenty female dogs, aged 6 to 12 years undergoing spinal fusion surgery postoperatively, all patients received opioid and continued on either gabapentin (5 mg/kg) or placebo 3 times per day for 5 days and pain was assessed using verbal numeric rating scale, they found that an initial preoperative loading dose and continued use of oral gabapentin decreased early total opioid consumption and pain scores in pediatric patients undergoing spinal fusion up to 2 days after surgery which compatible with result in our study [8].

Moreover, Ozgencil et al. made a study over 90 patients aged (18-70 years old) who were randomly assigned into three groups (pregabalin, gabapentin and placebo) of 30 patients each. Pregabalin 150 mg, gabapentin 600 mg and a placebo were administered every 12 h, two times pre and post-surgery and pain was assessed by VAS, their results showed that gabapentin and pregabalin are the preferred alternatives in postoperative analgesia and effective in controlling postoperative pain which agreed with the result of this study [13]. Although, Anju et al. made a randomized, double-blind, placebo-controlled study on 90 women aged (35-65 years old) undergoing abdominal hysterectomy who were anaesthetized in a standardized fashion. Patients received 300 mg pregabalin, 900 mg gabapentin or placebo, 1-2 h before surgery and pain assed by VAS they found that postoperative analgesia was better with 300 mg pregabalin than 900 mg gabapentin and placebo during the early recovery after abdominal hysterectomy and concluded that gabapentinoids are an effective tool in the treatment of postoperative pain of that study [14]. Another double blind, placebo controlled trial was done by Ahmad et al. on 90 patients aged (10-25) years undergoing tonsillectomy patients received either 20 mg/kg oral gabapentin(n=30),1.0 mg/kg rectal dicylofenac (n=30),or placebo (n=30) evaluation of postoperative pain was done by VAS for 24 h, the results showed that gabapentin and dicylofenac administration reduced the pain and the opioid consumption and the reduction was more in gabapentin group which consistent with our study [15].

Furthermore, Neerja B et al Who made a study on forty adult females (30-60) years undergoing total mastectomy for breast cancer, patients were randomly allocated into two groups, the gabapentin group received gabapentin 600 mg and the control group received placebo two h before the surgery. Postoperative analgesia was provided with intramuscular dicylofenac sodium and intravenous morphine on demand, they found that preoperative administration of gabapentin reduced the intraoperative anesthetic requirements, blunted the hemodynamic response to intubation, and reduced the postoperative opioid consumption which is compatible with this study [16]. In other study by Akgün et al. made a study on 46 healthy children aged 3-12 year old, they found that gabapentin premedication decreases postoperative 24 h analgesic consumption and attenuates emergence agitation after sevoflurane anesthesia which correspondent to this study [17].

In a conducted study by Abdolreza et al. who studied Seventy-eight primigravida women who scheduled for nonemergency cesarean delivery were enrolled in the study and separated into two groups. The control group received 12.5 mg of heavy bupivacaine 0.5 % plus 10 µg of fentanyl intrathecally and the case group received 300 mg of gabapentin orally 2 h before surgery and 12.5 mg of heavy bupivacaine 0.5 % intrathecally, they found that Pre-emptive use of gabapentin is a safe way to reduce postoperative pain and morphine consumption after cesarean section and can be an alternative for intrathecal opioid especially in patients who are sensitive to side effect of opioids which agreed with our study [18]. Also, Valiodlah et al. recorded that use of gabapentin before surgery can attenuate pain after laparoscopic gastric bypass surgery [19]. In our study we found that gabapentin lead to more stabilization of heart rate and mean arterial blood pressure which was an index for pain reduction. while Myung et al. found that in rats intrathecal and intraperitoneal gabapentin did not induce significant changes of hemodynamics over the 60 min compared to the baseline value [20]. Mausumi et al. found that gabapentin provide hemodynamic stability during laparoscopic surgery in both sexes and this compatible with our study [21].

Also, Vida et al. 30 patients aged 30-70 years underwent microlaryngeal surgery were included to their study. They found that gabapentin is effective in reducing the painful stimuli during laryngoscopy and intubation, hence attenuating the haemodynamic response which correspondent to our study [22].

Conclusion

Administration of gabapentin preoperatively significantly reduces postoperative pain and postoperative analgesia consumption in children under going orthopedic surgery. It also causes stability in hemodynamic status by decreasing stress response and anxiety.

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