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Analgesic effects of gabapentine in tonsillectomy

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Abstract

Objectives: To evaluate the preemptive effects of gabapentin on postoperative pain relief and its effect on meperidine consumption in patients undergoing tonsillectomy.

Methods: This study took place in King Abdulaziz Naval Base Hospital in the year 2009. Sixty patients ASA I and II were randomly assigned in a prospective randomized double- blind placebo-control clinical trial. Gabapentine 1200 mg or placebo was given orally two hours before induction of anesthesia to patients undergoing tonsillectomy under general anesthesia. Postoperative pain score was recorded on a visual analogue scale at 1, 3, 6, 12, 18 and 24 postoperative hours. Patients received meperidine 1 mg/ kg i.m once every 4 h if pain score ≥3 or if requested by the patient. Total dose of meperidine consumption was recorded.

Results: Thirty patients in the gabapentine group and 30 patients in the placebo group completed the study. Patients in gabapentine group had significantly lower pain score in comparison to placebo group. Total postoperative meperidine consumption in the gabapentin group was (48.8±33.9 VS 93.8 ± 54.6) in the placebo group (P< 0.001). There was higher incidence of nausea, vomiting, and use of antiemetic drugs in the placebo group.

Conclusion: Preemptive use of gabapentine decreased pain score and post operative meperidine consumption and reduced meperidine –related adverse effects in patients undergoing tonsillectomy under general anesthesia.

Introduction

Postoperative pain is a major factor that affect recovery from anesthesia and surgery. The treatment of postoperative pain after tonsillectomy presents a challenge. Tonsillectomy is associated with unacceptable intense pain during the first 24 hours after surgery[1]. Consistent delivery of first class postoperative pain control is still a major challenge. Opioids are inevitably associated with emesis and the risk of respiratory depression[2]. Local anesthetic techniques are often short lived and required interventional procedures, and the use of non steroidal anti-inflammatory drugs (NSAIDs) is limited by the well known complications and concerns. A combination of opioid and non opioid analgesic drugs improve the quality of postoperative analgesia and reduce opioid consumption as well as their related side effects[3].

Gabapentine, an anticonvulsant drug with structural analogue of gamma amino butyric acid which was introduced in the year 1994 particularly for partial seizures[4]. It alleviates pain and prevents acute nociceptive and inflammatory pain both in animals and volunteers ,especially when given before trauma[5,6].
Despite its name , gabapentine does not bind at the GABAa or GABAb receptors, however , it has a high binding affinity for the ά 2 δ subunit of the presynaptic voltage
gated calcium channels which inhibit calcium influx and subsequent release of

excitatory neurotransmitters in the pain pathway (as substance P and calcitonin gene–related peptide)[7].

Recently, several reports have indicated that preoperative administration of gabapentine may have a place in the treatment of postoperative pain after different surgical procedures; including, breast surgery[3], lumber discoidectomy surgery[2], and thyroid surgery[8] either given preemptively or post incision[9]. Gabapentine is a well –tolerated and safe drug[3,10]. Studies have shown a synergistic effect of gabapentine; as regard its analgesic action; with morphine in animal experiments and in humans[11]

Material and Methods

After approval of the Hospital Ethics Committee and informed written consents were obtained from all patients, 60 patients American society of anesthesiologists (ASA) I - II scheduled for tonsillectomy under general anesthesia were enrolled.
Patients were eligible if they were between 18 and 35 years old. Exclusion criteria were body weight exceeding 20% of ideal body weight, known allergy to gabapentine , chronic pain, daily intake of analgesics or corticosteroids, and impaired liver or kidney functions.
The use of visual analogue score (VAS) using a rule where 0 cm = no pain and 10 cm = the worst possible pain was explained to all patients included in this study.
Patients were randomly assigned to receive either 1200 mg oral gabapentine (neurontin 400 mg capsule; Pfizer, Germany) [Gabapentine group] or placebo [Placebo group] two hours before surgery.

Premedication was accomplished by midazolam 0.06 mgl/kg im, 30 min. before surgery. Anesthesia was induced with (propofol 2mg /kg i.v. , atracurium 0.5 mg/kg i.v. and fentanyl 1 ug /kg i.v.) . Anesthesia was maintained with sevoflurane 1% inspired at a fresh gas flow rate of 5L /min in combination with nitrous oxide 60 % in oxygen.
The concentration of agents was adjusted to maintain adequate depth of anesthesia (stable heart rate and blood pressure) within 20 % of the base line values.
Monitoring during anesthesia comprised of continuous electrocardiogram and heart rate, pulse oximetry, non invasive arterial pressure, measurements of end tidal CO2 and measurements of end tidal agent concentration. All parameters were recorded at five –minutes intervals.
At the end of surgery, residual neuromuscular block was antagonized with atropine 0.02 mg/kg and neostigmine 0.04 mg/kg i.v.
After tracheal extubation and awakening from anesthesia patients were transferred to the post anesthesia care unit (PACU).

After surgery, an anesthesiologist who was not part of the anesthesia team recorded the pain score at 1,3,6,12,18,24 hour postoperatively, the maximum pain score at different time intervals for each patients were considered for statistical analysis. Meperidine 1 mg /kg i.m. every 6 h was given for postoperative pain relief if pain score ≥ 3 or if requested by the patient. The worest pain score was recorded at the first dose of meperidine injection. The time of first dose of meperidine injection and the total consumption of meperidine within 24 hours is calculated.

Post operative side-effects related to meperidine, as nausea and vomiting, respiratory depression, dizziness and somnolence were recorded in the (PACU) and in the ward . Nausea was recorded for each patient in a four points scale (none ,light, moderate or severe) .Sedation was also recorded on a sedation score using a four points verbal rating scale (VRS) in which 0 = nil, 1 = mild, 2 = moderate, 3 = severe. Patients grading for postoperative analgesia was recorded where

0 = nil, 1 = mild, 2 = moderate, 3 = good, 4 = excellent. Side effects were treated as required.

Data were statistically described in terms of mean ± standard deviation (± SD) or frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison between the 2 studied groups was done using Student *t* test for independent samples in comparing quantitative data. For comparing categorical data, Chi square (χ^2) test was performed. Yates correction was used in stead when the expected frequency is less than 5. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program.

Results

Sixty consecutive patients completed the study. There were no demographic data and surgical time differences among both groups as regards to age (31.4 ± 7.7)yr, (29.8 ± 6.5)yr , body weight (66.7 ± 8.6) kg , (68.6 ± 7.8) kg , height (163 ± 8.8) cm , (162.3 ± 7.6) cm and duration of surgery (61 ± 23.4) min , (54 ± 20.8) min (Table 1).There were no differences among the two groups as regards intraoperative (mean blood pressure, heart rate, oxygen saturation) at any of the measured time.

In comparison with placebo, patients in the gabapentine group had significantly lower VAS scores in all time intervals (1,3,6,12,18,24) hours postoperatively. (4.3 ±1.1 , 2.8 ± 0.6) , (3.6 ± 0.9 , 2.2 ±0.5) , (3.2 ± 0.8 , 2.1 ± 0.6) , (2.6 ± 0.7 , 1.7 ± 0.4) , (2.2 ± 0.5 , 1.1 ± 0.8) , (2.1 ± 0.4 , 1.0 ± 0.7) (fig 1), (Table 2)

The mean time to first analgesic administration was longer in the patients included in the gabapentine group. The total meperidine consumption after surgery in the first 24 hours in the gabapentine group was significantly less (48.8 ± 9.7, 93.8 ± 8.4)
(Table 3). Patient satisfaction with their postoperative pain management(score = 3 - 4) was significantly greater in the gabapentine group compared with placebo (26 - 20) patients respectively (Table 3).

As regards side effects during the postoperative period we found the incidence of dizziness was insignificant between both groups (5 and 6 patients) in placebo and gabapentine groups respectively. There is higher incidence of nausea ,vomiting and the use of antiemetic medication in placebo group in comparison with gabapentine group
(12 , 5), (8 , 3) , (11 , 3) respectively (Table 4).

Table 1: Demographic data and operative duration

	Gabapentine n = 30	Placebo n = 30	*p* value
Age (years)	31.4 ± 7.7	29.8 ± 6.5	0.787
Gender (male/female)	37/23	33/27	0.681
Body weight (kg)	66.7 ± 8.6	68.6 ± 7.8	0.707
Height (cm)	163.2 ± 8.8	162.3 ± 7.6	0.763
Duration of surgery (min)	61 ± 23.4	54 ± 20.8	0.728

Values are expressed as mean +/- SD or absolute number

Table 2: Postoperative (VAS)

	Gabapentine n = 30	Placebo n = 30	*p* value
1 hour	4.3 ± 1.1	2.8 ± 0.6	< 0.001
3 hours	3.6 ± 0.9	2.2 ± 0.5	< 0.001
6 hours	3.2 ± 0.8	2.1 ± 0.6	< 0.001
12 hours	2.6 ± 0.7	1.7 ± 0.4	< 0.001
18 hours	2.2 ± 0.5	1.1 ± 0.8	< 0.001
24 hours	2.1 ± 0.4	1.0 ± 0.7	< 0.001

Values are expressed as mean +/- SD

Table 3: Postoperative analgesia, meperidine requirement and related side effects

	Gabapentine n = 30	Placebo n = 30	*p* value
Time to 1st meperidine injection (hr)	6.6 ± 4.2	2.4 ± 2.0	< 0.001
Total meperidine consumption (mg)	48.8 ± 9.7	93.8 ± 8.4	< 0.001
Worst pain score	4.0 ± 2.4	6.0 ± 1.4	< 0.001
Meperidine related side effects			
- Nausea	5 (16.67%)	13 (43.33%)	0.049
- Satisfaction	27 (90.00%)	19 (63.33%)	0.033

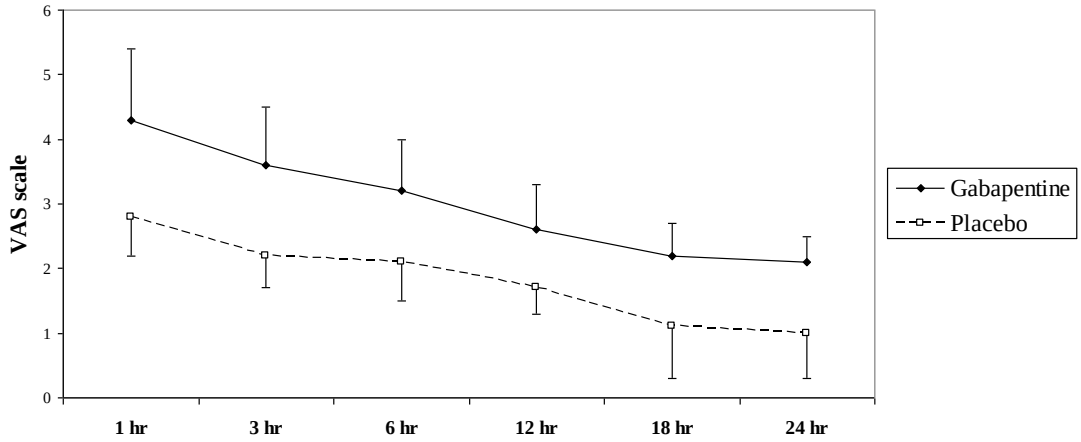
Values are expressed as mean +/- SD or absolute number

Table 4: Side effects related to meperidine in both groups

	Gabapentine n = 30	Placebo n = 30	*p* value
Nausea			
- Mild	3 (10.00%)	7 (23.33%)	
- Moderate	2 (6.67%)	4 (13.33%)	0.642
- Severe	0 (0.00%)	2 (6.67%)	
Vomiting	2 (6.67%)	9 (30.00%)	0.045
Use of anti emetics	3 (10.00%)	11 (36.67%)	0.033
Dizziness	6 (20.00%)	5 (16.67%)	1.000
Sedation score:			
- Mild	4 (13.33%)	3 (10.00%)	
- Moderate	2 (6.67%)	1 (3.33%)	0.497
- Severe	0 (0.00%)	1 (3.33%)	
Somnolence	2 (6.67%)	1 (3.33%)	1.000

Values are expressed as absolute number and percentage.

Figure 1: Post operative (VAS) between studied groups.



Discussion

The results of this study showed that a single oral dose of 1200 mg gabapentine given two hours before tonsillectomy decreased post operative pain score, reduced the need of postoperative meperidine consumption during the first 24 hours postoperatively, and decreased meperidine related side effects compared with placebo.

The main aim of combining different analgesic drugs and techniques is to obtain synergistic or additive actions that allow a smaller dose of each agent to be used and thereby improve the safety profile. This can be achieved by combining analgesics acting at different locations.

Gabapentine reduced tactile allodynia (which is α – amino – 3 – hydroxyl – 4- isoxazolaproprionate AMPA) after incision[12] and reduced mechanical hyperalgesia (which is N-methyl – D – aspartate mediated NMDA) in a rat model of postoperative pain[13]. Mechanical hyperalgesia surrounding the wound postoperatively together with induced ,secondary hyperalgesia share a common mechanism, and central neuronal sensitization might contribute to some aspects of postoperative pain therefore, antihyperalgesic drugs such as gabapentine

The lower scores of postoperative nausea and vomiting in the gabapentine group might be due to the diminished need for postoperative meperidine consumption may have a role in postoperative pain control, and combination of antinociceptive

and antihyperalgesic drugs may provide synergistic effects[14]. Pretreatment with gabapentine also blocked the development of hyperalgesia, suggesting a preventive effect of gabapentine, and a selective effect on the nociceptive process involving central sensitization[15].

Previous clinical studies with gabapentine for postoperative analgesia have shown promising results. Oral gabapentine 1200 mg administered one hour before surgery decreased pain scores in the early postoperative period and postoperative morphine consumption in spinal surgery patients, while decreasing morphine-associated side effects[16]. Another study demonstrated that a single dose of 1200 gabapentine given 2 to 2.5 hour before induction of anesthesia reduced the need for additional postoperative pain treatment by 40 % during the first 20 postoperative hours in patients undergoing vaginal hysterectomy[17]. Ganter *et al*[18], used gabapentine for diffuse intractable pain following face lift surgery and reported dramatic improvement in postoperative pain. Also AL-Mujadi *et al*[8], found preoperative gabapentine decreases pain scores and postoperative morphine consumption in patients following thyroid surgery.

and because of an antiemetic effect of gabapentine[17]. Our results supported by most recent meta-analysis done by using databases of 22 randomized, control trials by Tiippana *et al*[19] who concluded that gabapentine is effective in reducing pain intensity, opioid consumption and opioid – related adverse effects after surgery and concluded that gabapentine has very few adverse effects.

The dose we studied (1200 mg) is within the limits of a single dose in the treatment of neuropathic pain, as the recommended dose is 300 to 1200 mg three times daily[3]. In previous studies the dose of gabapentine ranged from 300 mg to 1200 mg preoperatively. The studies which evaluate the lowest doses yield the least impressive reduction in analgesic consumption[2,11,20]. A review of 16 studies by Ho *et al*, demonstrated that a single preoperative dose of gabapentine (1200 mg) reduced pain intensity, opioid consumption and opioid related adverse effects for the first 24 h postoperatively[21].

Gabapentine has been reported as an anxiolytic drug in previous studies[22,23]. Reducing preoperative anxiety with gabapentin may have contributed to the improved postoperative analgesia and to reduced meperidine requirement because there is possible association between preoperative anxiety and post operative pain[24].

Dizzeness and somnolence have been demonstrated to be the commonest side effects of gabapentine in previous controlled studies of chronic pain[3,10,25,26,27]. These studies however, were usually performed in patients with long term gabapentine use. In this study only one single oral dose 1200 mg was used and there was no significance difference between both groups as regards side effects related to gabapentine (dizzeness and somnolence), non of the patients required treatment and the side effects were well tolerated. However, a meta-analysis done by Seib and Paul[28], concluded that gabapentine given preoperatively decrease pain scores and analgesic consumption in the first 24 hours after surgery, but could not demonstrate a significant reduction in the incidence of side effects but this results needs further evaluation due to the small number of patients enrolled.

In conclusion gabapentine used preemptively decrease pain scores in post operative period of tonsillectomy and decrease postoperative meperidine consumption and meperidine related side effects. Gabapentine could be a useful adjunctive for pain management postoperatively.

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تأثير عقار الجابابنتين كمسكن للألم فى حالات استئصال اللوزتين

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الغرض من الدراسة

أجريت هذه الدراسة لتقيم التاثير الوقائى للجابابنتين لتسكين الألأم بعد عملية استئصال اللوزتين وكذلك تأثيره على استهلاك الميبيريدين عند المرضى الذين تجرى لهم عملية استئصال اللوزتين

أجريت هذه الدراسة فى المستشفى العسكرى بقاعدة الملك عبد العزيز البحرية عام **2009.** ستون مريضا ASA 1و2 اختيروا عشوائيا . جابا بنتين 1200مجم تم اعطاءه بالفم ساعتين قبل بداية التخدير للمرضى الذين ستجرى لهم عملية استئصال اللوزتين بتخدير كلى. ومن ثم تم تسجيل الألأم بعد العملية خلال 24,18,12,6,3,1 ساعه

وأيضا تم اعطاء المرضى ميبيردين 1مجم / كجم بالعضل كل 4 ساعات وذلك لو كان معدل الألم أكثر من أو يساوى 3 أو اذا طلبه المريض 0 وتم تدوين الجرعة الكليه المعطاه للمريض0

النتائج

تم اجراء الدراسه على 30 مريض من مجموعة جابابنتين و 30 مريض من المرض الذين اعطى لهم علاج تمويهى. المرضى بمجموعة جابابنتين كان لديهم ألم أقل بدرجة ملحوظة من المجموعة التى أعطيت علاج تمويهى .الاستهلاك الكلى للمبيريدين بعد العملية فى مجموعةجابابنتي9 33, VS 54,6 + 93,8) فى مجموعه العلاج التمويهى (ب < 0,001) كان هناك معدل اعلى من الغثيان والقئ واستخدام ادويه للقئ فى مجموعة العلاج التمويهى

ويشير هذا البحث الى ان الاستخدام الوقائى للجابابنتين يقلل من الألم وكذلك استهلاك الميبيردين بعد عمليه استئصال اللوزتين وكذلك تجنب الأثار الضاره