Original Article

Gabapentin May Relieve Post-Coronary Artery Bypass Graft Pain: A Double Blind Randomized Clinical Trial

M Soltanzadeh[1], A Ebad[1], MR Pipelzadeh[1], SK Tabatabaei[1], M Dehghani Firouzabadi[1], A Vasigh[1], MA Soltanzadeh[2], A Heidari[3], A Ramazani[3], H Haybar[4]

[1]Department of Anesthesiology of Imam Khomeini Hospital, Ahwaz Jundishapur University of Medical sciences, Ahwaz [2]Shiraz University of Medical Sciences, Shiraz [3]Department of Cardiac surgery, Imam Khomeini Hospital, Ahwaz Jundishapur University of Medical sciences, Ahwaz [4]Department of Cardiology, Imam Khomeini Hospital, Ahwaz Jundishapur University of Medical sciences, Ahwaz, Iran

Abstract

Background: One of the most common complaints after coronary artery bypass graft (CABG) is post-operative pain. Gabapentin is an anticonvulsant and antineuralgic agent.

Objective: To evaluate the analgesic effect of preemptive gabapentin on post-operative pain and morphine consumption after cardiac surgery.

Methods: A double-blind randomized clinical trial was conducted on 60 male candidates for CABG. The patients were divided into two groups—the gabapentin (n=30) and the control group (n=30). The test group received 800 mg gabapentin orally two hours before the surgery followed by 400 mg of the drug two hours post-extubation. The control group received placebo instead. Then severity of pain was recorded according to an 11-point visual analog pain scale. The amount of morphine consumed, its side effects and hemodynamic changes were also recorded during and at 2, 6, 12, 18 and 24 hours after extubation.

Results: The mean±SD cumulative morphine consumption at the first 24 hours after extubation in gabapentin group was 0.9±1.5 mg while it was 1.5±4 mg for the control group. Therefore, gabapentin group consumed 38% less than the control group (P=0.01). The pain scores during rest and coughing at 2, 6, and 12 hours after extubation were also significantly lower in the gabapentin group compared with the control group (P=0.02). The mean±SD mechanical ventilation time was 5.4±1.7 hours for gabapentin group and 1.6±4.4 hours for the control group (P=0.035). The other variables including hemodynamic changes (HR, SBP and DBP), and incidence of nausea, vomiting and respiratory depression showed no significant difference between the studied groups within 24 hours after extubation.

Conclusion: Oral pre-medication with gabapentin before CABG significantly reduces post-operative pain and morphine consumption in adult cardiac surgery.

Keywords: Pain; Coronary Artery Bypass Graft; Gabapentin

Manuscript received: May 25, 2011; Accepted: July 17, 2011

Iran Cardiovasc Res J 2011;5(3):79-82

Introduction

The most common medical complaint is the pain.[1] Post-operative pain may produce a range of acute and chronic pathological effects.[2] Pain reduces person performance.[3] Adequate pain control after cardiac surgery plays an important role in maintaining hemodynamic stability, low myocardial oxygen consumption, and low incidence of ischemic events.[4] Opioid analgesics have essential role in the treatment of post-operative pain. These drugs generally exert their analgesic effects through μ-receptors in the central nervous system (CNS), although there is evidence that opioids may also act at peripheral opioid receptors. The analgesic ability of opioids to reduce pain is typically limited by the development of tolerance or opioid-related side effects such as nausea, vomiting, sedation or respiratory depression.[5]

Gabapentin is an anticonvulsant and antineuralgic agent and its mechanism of action is unknown. Gabapentin does not interact with GABA receptors, is not metabolized to GABA agonist or to GABA, and neither it inhibits GABA uptake or degradation. Gabapentin is not metabolized and its clearance is directly proportional to creatinine clearance.[6] The anticonvulsant properties

Correspondence: M Soltanzadeh, Heart Operating Room, Golestan Hospital, Ahwaz, Iran
Tel:+98-611-374-3017
E-mail: soltanzadeh-m@ajums.ac.ir

of gabapentin are unique.[7] In treatment of neuropathic pains, gabapentin is very effective due to fewer side effects and is often the first choice for the treatment of neuropathic pains.[8] The analgesic effects of gabapentin after surgery are reported differently.[9,10] Most studies have shown that taking gabapentin before surgery reduces post-operative morphine consumption,[11] but some other studies reported no effect of gabapentin on reduction of the post-operative pain or morphine consumption.[12] This study was conducted to evaluate the gabapentin effect on post-operative pain and opioid analgesic consumption.

Patients and Methods

The protocol of this double blind randomized clinical trial was approved by the Institutional Ethics Committee at Jundishapur University of Medical Sciences, Ahwaz, southwestern Iran. After taking written informed consents from 60 men aged 20-70 years who were candidates for coronary artery bypass graft (CABG) surgery, the patients were enrolled in this study. The exclusion criteria included a history of chronic use of analgesics (nonsteroidal anti-inflammatory drugs, opioids, or paracetamol), tranquilizer, anticonvulsant or antidepressant drugs; alcohol dependence; malabsorption; hepatic or renal insufficiency; emergency surgery; previous cardiac surgery; left ventricular dysfunction (ejection fraction <40%); pre-operative use of inotropic agents or intra-aortic balloon pump; and allergy to the drugs used in this study. Patients who needed a redo sternotomy were also excluded from the study.

By using a randomized closed-envelope system, the patients received either oral gabapentin, 800 mg (n=30) or placebo (n=30) two hours before the surgery, followed by 400 mg oral gabapentin or placebo two hours after extubation. All patients received intramuscular morphine 10 mg and 25 mg promethazine before transferring to the operating room. On arrival, in the operating room, the baseline arterial blood pressure, heart rate, CVP, peripheral oxygen saturation and blood gas parameters were evaluated by standard monitors. Anesthesia was induced with diazepam (0.1–0.2 mg/kg), fentanyl (3–10 μg/kg), atracurium (0.5–0.6 mg/kg) and thiopental (STP 2 mg/kg). After endotracheal intubation, all patients were mechanically ventilated to maintain an end-expiratory CO_2 pressure of 34–36 mm Hg. Anesthesia was initially maintained with midazolam, 0.1 mg/kg/hr and fentany l5 μg/kg/hr and if required isoflurane 0.4% inspired at a fresh gas flow with 50% oxygen. Patients were then transferred to cardiac surgery ICU under anesthesia. In the ICU, mechanical ventilation support was started for all patients. Criteria for weaning from the mechanical ventilation were hemodynamic stability, absence of significant surgical bleeding, oxygen saturation >95% with an FiO_2 <0.5% and PEEP<5 cm H_2O, $PaCO_2$<45 mm Hg, and pH>7.35 on pressure-support ventilation for one hour. As soon as the patients followed verbal commands, extubation was performed. After extubation, pain was assessed based on a numerical rating scale (NRS) in which zero corresponds to analgesia and 10 corresponds to the maximum pain imaginable. Post-operative pain was assessed at 2, 6, 12, 18 and 24 hours after extubation. An additional 2 mg morphine was administered intravenously if requested by the patient (NRS≥3) as rescue analgesia. Drowsiness of the patients were evaluated by sedation score criteria where zero corresponds to "restlessness," one "quiet alert,"

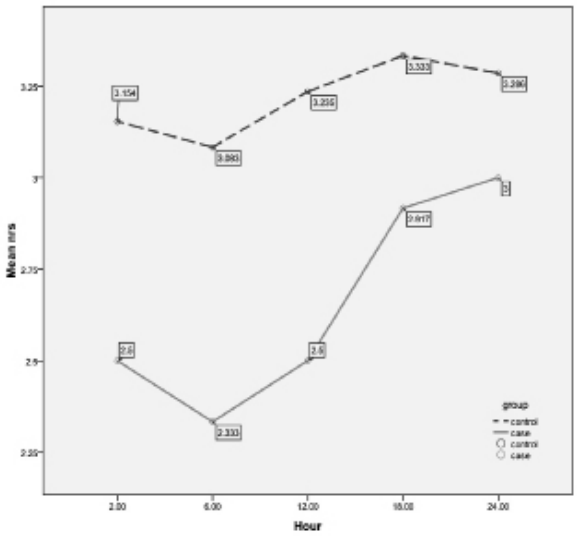

Figure 1: NRS scores of the control and test groups at rest (p=0.01)

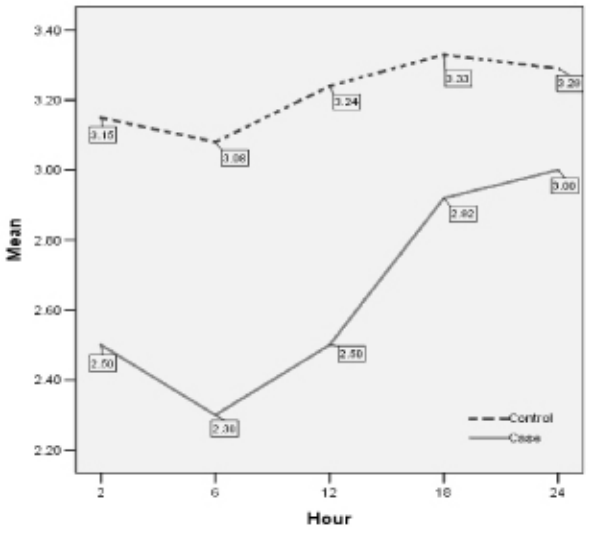

Figure 2: NRS scores of the control and test groups while cough (p<0.02)

Table 1: Demographic and clinical data of studied patients

Parameter	Control Group (n=30)	Gabapentin Group (n=30)	P value
Mean±SD age (yrs)	55.2±8.1	58.2±8.3	0.16
Mean±SD weight (kg)	70.7±9.3	73.7±10.4	0.258
Mean±SD BMI (kg/m^2)	24.4±2.9	25.6±3.3	0.16
Mean±SD number of grafts	2.7±0.47	2.8±0.40	—
History of hypertension % (n/N)	67 (20/30)	60 (18/30)	0.75
History of diabetes mellitus % (n/N)	13 (4/30)	10 (3/30)	0.68
Mean±SD cardiopulmonary bypass time (min)	102±6	108±7	—
Mean±SD operation time (h)	4±0.5	4.4±0.5	—
Mean±SD ICU length of stay (d)	2.5±0.6	2.4±0.6	—
Mean±SD interval between doses of gabapentin or placebo (h)	11.8±1.3	12.8±2.1	

two "sleepy but response to verbal stimulation," three "response to painful stimuli" and four corresponds to "no response to verbal stimulation or touch." Respiratory depression was defined as a respiratory rate <8 breaths/min lasting 10 min or an oxygen saturation <90% without oxygen supplementation. Statistical analyses of the data were performed by SPSS ver 17.0.

Results

The studied groups were comparable in terms of demographic and operative variables (Table 1). Pain scores, both at rest and during coughing at 2, 6, and 12 hours after extubation were significantly lower in the gabapentin group compared with the control group (P=0.02) (Figs 1,2).

The mean±SD total morphine consumption was 2.5±0.9 mg in gabapentin group-38% lower than that in the control group (4±1.5 mg, P=0.01) at 24 hours (Fig 3). The mean morphine consumption after extubation were also significantly (P<0.001) lower in gabapentin group than in the control group at 2, 6, and 12 hours interval (P<0.001) (Fig 4).

Hemodynamic changes (HR, SBP and DBP), and incidence of nausea, vomiting and respiratory depression within 24 hours, among the test and control groups showed no significant difference.

The post-operative mechanical ventilation was significantly (P=0.03) longer in gabapentin (5.4±1.7 hours) than in the control group (4.4±1.6 hours).

The number of oversedated patients (a sedation score >2) was higher in gabapentin group at 2, 6 hours of study compared with the placebo group (P<0.05).

The mean±SD interval after extubation to the first request for analgesic was 4.8±1.6 hours for the control group and 8.2±2.7 hours for the test group (P<0.001). Sedative drug requirements within two hours of extubation decreased by 30% in gabapentin group compared to the control group (P<0.001).

Discussion

We found that pre-operative oral administration of gabapentin decreases pain significantly at 6 and 12 hours post-extubation at rest and while cough. Administration of gabapentin reduced 38% morphine consumption 24 hours after extubation. Sedative effects at 2 and 6 hours post-extubation

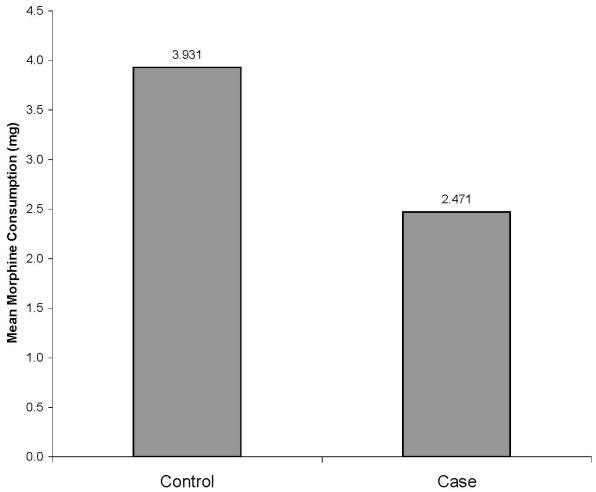

Figure 3: The mean morphine consumption in each patient among the test and control groups 24 hours post-extubation

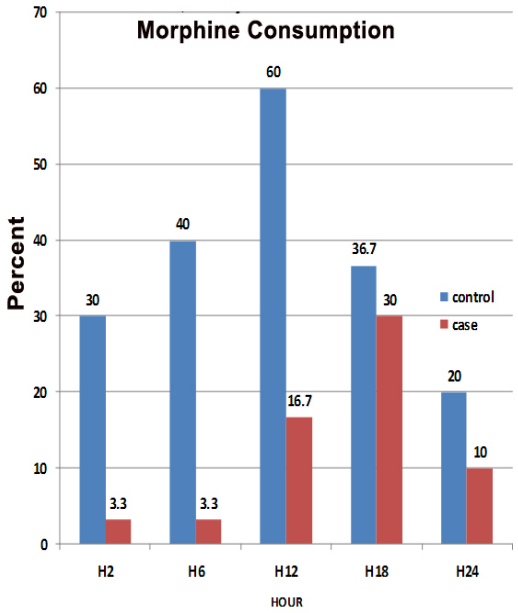

Figure 4: The morphine consumption among the test and control groups at different times post-extubation.

in gabapentin group, however were higher than the control group. The increased sedative effects of gabapentin group would be due to its synergistic effect with benzodiazepines and opioids administered during general anesthesia. The mean duration of ventilation in gabapentin group was almost 1.1 hours longer than that in the control group. The mean time for the first need for opioid after extubation was significantly lower in gabapentin than the control group (P=0.001).

The study by Ferdi Menda, *et al*, showed that by giving oral gabapentin at a dose of 600 mg two hours before cardiac surgery, morphine consumption after extubation would be reduced significantly (by 57%) compared to the control group.[13] Nonetheless, in our study and the study by Ferdi Menda that oral gabapentin was administered before the operation, reduction in morphine consumption was lower than that reported by Ebadi, *et al*, who applied thoracic epidural anesthesia to reduce morphine consumption after CABG surgery.[14]

There was no significant difference (P=0.057) between the incidence of nausea in gabapentin and the control groups in our study, though it was in Ferdi's study (P=0.02).

Conclusion

Oral gabapentin at a dose of 800 mg given two hours before CABG followed by 400 mg at least two hours after extubation, significantly reduces post-operative morphine consumption and pain both at rest and while cough, without clinically considerable side effects.

Acknowledgements

This study was supported by Ahwaz Jundishapur University of Medical Sciences.

References

1. Waldman SD. Pain Management. 2nd ed. Philadelphia: Saunder's; 2007.p.225-55.
2. Miller RD. Text Book of Anesthesia. 7th ed. Philadelphia: Churchill Livingeston; 2010.p. 2758-9.
3. Watson M, Lucas C, Hoy A, Back I. Oxford Handbook of Palliative Care. 3rd ed. NewYork: Oxford University Press; 2005.p. 187.
4. Chaney MA. How important is postoperative pain after cardiac surgery? *J Cardiothoracic Vasc Anesth* 2005;**19**:705-7. [PMID:16326291]
5. Power I. Recent advances in postoperative pain therapy.*Br J Anaesth* 2005;**95**:43-51 [PMID:15579488].
6. Sills GJ. The mechanisms of action of gabapentin and pregabalin. *Curr Opin Pharmacol* 2006;**6:**108-13. [PMID: 16376147]
7. Trevor AJ, Katzung BG. Katzung &Trevor's Pharmacology: Examination & Board Review. 8th ed. USA: Mc Graw Hill; 2008.p.201-3.
8. Ballantyne j. The Massachusetts general handbook of pain management. 3rd ed. USA: Lippincott Williams & Wilkins; 2006.p. 236-8.
9. Takmaz SA, Kaymak C, Pehlivan BS, Dikmen B. Effect of preoperative 900 and 1200 mg single oral dose of gabapentin on postoperative pain relief and tramadol consumption in open cholecystectomy surgery. *Agri* 2007;**19**:32-8. [PMID:18095197]
10. Hara K, Saito Y, Kirihara Y, Yamada Y, Sakura S, Kosaka Y. The interaction of antinociceptive effects of morphine and GABA receptor agonists within the rat spinal cord. *Anesth Analg* 1999;**89**:422-7. [PMID:10439759]
11. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. *Anesthesiology* 2002;**97**:560-4. [PMID:12218520]
12. Adam F, Menigaux C, Sessler DI, Chauvin M. A Single Preoperative Dose of Gabapentin (800 Milligrams) Does Not Augment Postoperative Analgesia in Patients Given Interscalene Brachial Plexus Blocks for Arthroscopic Shoulder Surgery. *Anesth Analg* 2006;**103**:1278-82. [PMID:17056969]
13. Menda F, Köner O, Sayın M, Ergenoğlu M, Küçükaksu S, Aykaç B. Effects of Single-Dose Gabapentin on Postoperative Pain and Morphine Consumption After Cardiac Surgery. *J Cardiothorac Vasc Anesth* 2010;**24**:808-13. [PMID:20056448]
14. Ebadi A, Soltanzadeh M, Ramazani A. Application of thoracic epidural analgesia in patients undergoing coronary artery bypass graft surgery. *Biochemical and cellular archives* 2007;**7**:261-4.