ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
Research Article
www.ijptonline.com

EFFECT OF PRE-EMPTIVE GABAPENTIN VS DICLOFENAC ON POSTOPERATIVE PAIN FOLLOWING DACRYOCYSTORHINOSTOMY UNDER GENERAL ANESTHESIA

Khalili M[1], Modir HE[1*], Rashidi A[2], Sadeghi sedeh B[3], Kashani M[4]
[1]Assistant Professor, Anesthesiologist, Arak University of Medical Sciences, Arak, Iran.
[2]Assistant Professor, ophthalmologist, Arak University of Medical Sciences, Arak, Iran.
[3]Assistant Professor, Epidemiologist, Arak University of Medical Sciences, Arak, Iran.
[4]General Practitioner, Arak University of Medical Sciences, Arak, Iran.
Email: modir.he@gmail.com

Received on 04-03-2016 *Accepted on 25-03-2016*

Abstract

Introduction: Postoperative pain control can have a significant effect on patient recovery. Gabapentin and non-steroidal anti-inflammatory drugs can reduce postoperative pain. The aim of this study is to compare gabapentin and diclofenac in their ability to control pain after dacryocystorhinostomy. **Methods:** In this clinical trial, 62 patients undergoing open dacryocystorhinostomy under general anesthesia, were randomly allocated into three groups. The first group received 300 mg gabapentin, the second group 100 mg diclofenac and the third group received placebo capsules 30 minutes before induction of anesthesia. Pain score was measured by visual analog scale (VAS)at 60, 120, 180 and 240 minutes after conclusion of surgery.In the case ofopioid injection for post-operative pain control, it was also recorded. **Results:** Pain score at 60 and 120 minutes was significantly lower in gabapentin and diclofenac groups compared to placebo. Gabapentin, more effectively than diclofenac and placebo, controlled pain in third and fourth hours post-operatively. During the 3rd and 4th hours, diclofenac and placebo did not differ statistically in controlling the pain. The need for opioid injection was not significantly different between groups(x^2=0.16). **Conclusions:** Both gabapentin and diclofenac can control pain in early hours after dacryocystorhinostomy. Due to an increased pain during the 4th hour, it is suggested that higher doses of pre-operative gabapentin, or combined pre and post-operative doses be used.

Keywords: Dacryocystorhinostomy, Diclofenac, Gabapentin

Introduction: Despite all efforts to control pain after surgery, it is still a serious problem in patients. Severe pain can cause adverse physiological effects on the body such as increased sympathetic activity, increased heart rate and blood

pressure, coronary ischemia, deep venousthrombosis, pulmonary disorders and at electasis (1). Opioid analgesics are considered as basis to control pain after surgery. Because of their known side effect of respiratory depression (which can potentially cause patient mortality) many efforts have been done to replace them with less hazardous medications and methods of pain control (4-1). In fact, the ultimate goal is finding an analgesic drug with a great effect and much fewer side effects.

Non-steroidal anti-inflammatory drugs are also frequently used for pain control after surgery. Because of their adverse effects on renal and digestive systems, their use is limited and it seems that the use of other drugs with less side effects can be useful (5, 6).

One of the drugs which are recently used for this purpose is gabapentin. Gabapentin is a structural analogue of Aminobutyric acid which was introduced for the first time in 1994 as an antiepileptic drug, especially for partial seizures (7). Several studies have shown that the use of gabapentin can reduce postoperative pain (8-10).

Gabapentin decreases the excitability of neurons in the posterior rami of spinal cord(7). It is believed that gabapentin decreases calcium in nerve endings by binding to alpha2-delta subunitsof voltage-sensitive calcium channels. This results in reduced release of neurotransmitters for pain. Other mechanisms involved in pain control by this drug are its probable transaction with NMDA receptors, sodium channels, monoaminergic pathways and opioid system (14-11).

Among surgeries, dacryocystorhinostomy causes mild to moderate pain and use of opioids in pain management at this level can cause respiratory complications, nausea, vomiting and urinary retention, especially in the older age group (15). Therefore, use of other drugs instead of opioidscould be a convenient and practical solution in controlling pain. Hence this study was designed to compare gabapentin and diclofenac in pain management after dacryocystorhinostomy surgery.

Materials and Methods

In this clinical trial, 62 patients who were candidates for open dacryocystorhinostomy surgery under general anesthesia in Amirkabir hospital were enrolled after obtaining written consent. Patients suffering from psychosis, Alzheimer, cognitive disorders, addiction to alcohol or drugs, pregnancy, renal and gastrointestinal problems, diabetes and a history of allergies were not included in the study. The study was approved by the Ethics Committee of Arak University of Medical Sciences by number 9-143-92. It was also registered in Iranian Registry of Clinical Trials by numberIRCT2016061114056N7. After obtaining demographic data, patients were randomly allocated into three groups of gabapentin, oral diclofenac sodium and placebo. That means 100cc water with either 300mg gabapentin or 100mg oral

diclofenac or handmade capsules containing starch as placebo were given to the patients about half an hour before induction of anesthesia.

For premedication,1.5 µg/kg fentanyl and 0.04mg/kg midazolam, and for induction and airway control 2.5mg/kg propofol and 0.5mg/kg atracurium were used in all patients.

Patients' airways were controlled using laryngeal mask airway and for all patients mechanical ventilation was established using a gas mixture of oxygen and nitrous oxide (N2O) at a 50/50 ratio. For maintenance of anesthesia propofol infusion at a rate of 10-30cc/hr (according to the hemodynamics for each patient) was used. Pain intensity was measured using VAS scale at 60, 120, 180 and 240 minutes after the conclusion ofanesthesia and entering the post anesthesia care unit. In the case of intolerable pain, intravenous pethidine was prescribed for the patient. The pain scores of patients and also the need for pethidine in each patient was recorded. Data were analyzed using SPSS statistical software version 21.

Results

A total of 62 patients were studied; 13 women and 8 men in gabapentin group, 9 women and 11 men in diclofenac group and 12 women and 9 men in placebo group. There was no significant difference between sex variable in three groups (chi-square = 0.0535).

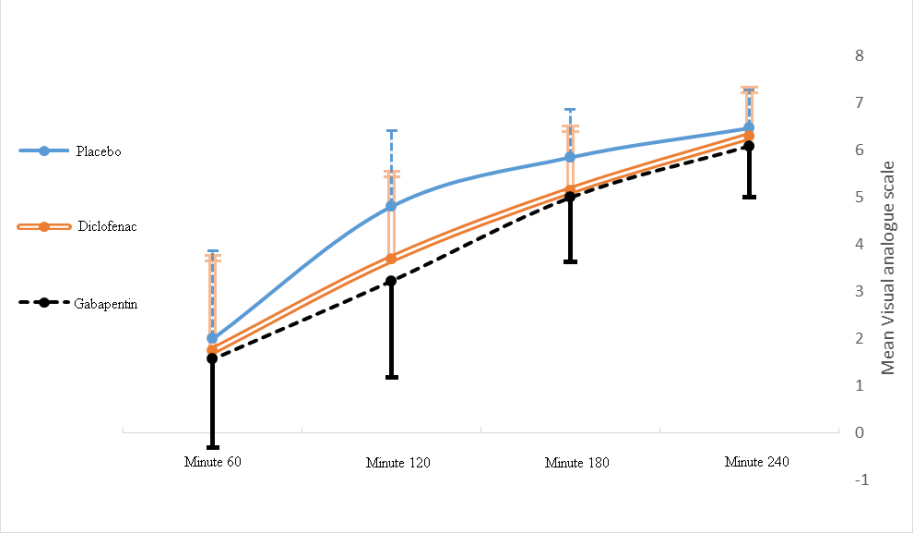
The average age of patients was 49.33±16.1 years in gabapentin group, 52.75±15.57 years in diclofenac group and 54.23±13.83 years in placebo group. There was no significant difference between groups in terms of age (p=0.334). The average weight of the patients was 66.09±9.8 in the gabapentin group, 65.75±10.18 in diclofenac group and 69.23±8.44 in placebo group and in terms of average weight, again there was no significant difference between groups (p=0.273).

The average pain scores of patients in the groups at different times are shown in diagram 1. Based on the analyzed data, the average pain score at the end of the 60^{th} minute in the gabapentin group compared with diclofenac was not statistically significant (p=0.92), but the pain score in gabapentin group (p=0.048) and diclofenac group (p=0.03) was significantly less than the placebo group. As it is shown in the diagram, the average pain score in minute 120 in two groups of gabapentin and diclofenac was significantly lower than the placebo group ($p<0.05$) but there was no significant difference between two groups of gabapentin and diclofenac ($p>0.05$).

The average pain score in minute180 after surgery was 5±1.37, 5.15±1.3 and 5.85±1.01 in gabapentin, diclofenac and placebo groups respectively. Gabapentin group had significantly less pain scores compared to placebo group (p=0.045), but gabapentin and diclofenac as well as diclofenac and placebo groups were not significantly different ($p>0.05$).

Comparison of the average pain scores in minute 240, is the same as the minute 180 in three groups, that is the pain score in gabapentin group compared to placebo group was significantly less (p=0.048), but gabapentin and diclofenac as well as diclofenac and placebo groups were not significantly different (p>0.05).

In examining the need for intravenous pethidine after the surgery it was found that 1 person in gabapentin group, 2 persons in diclofenac group and 5 persons in placebo group had received pethidine after surgery because of intolerable pain. The results showed that patients ingabapentin and diclofenac groups needed pethidine injections less frequently than patients in the placebo group, but this difference was not statistically significant (chi-square=0.16).



Graph (1): The average of patients' pain scores in three groups of placebo, diclofenac and gabapentin at different times

Discussion and Conclusion:

The results of our study showed that prescription of 300mg gabapentin compared to placebo significantly decreases pain at different time intervals after dacryocystorhinostomy surgery. According to the diagram 1 the placebo group's pain score progressively increases during the first post-operative 2 hours and then its upward slope slightly diminishes, making a relative plateau. In gabapentin and diclofenac groups, compared to the placebo group, the pain scores increase with an almost constant slope during the entire study time (until the 4th hour), probably due tovanishing effects of the opioid anesthetics and the time-dependent decreasing blood levels of gabapentin and diclofenac. Of note, pain scores of these two drugs during the whole study time are well below the numbers for placebo group. In our study the need for opioids in the postoperative period in gabapentin group was lower than other groups but this difference was not statistically significant. In the case of the analgesic effect of gabapentin there are contradictory results. In line with the results of this study, Panah Khahi et al, in their study concluded that prescription of 300mg gabapentin before orthopedic

surgery can reduce pain 2 hours after surgery (8). Moreover, another study has shown that prescription of 1200mg gabapentin one hour before intravenous regional anesthesia for hand surgery can control acute pain and also reduce the need for morphine (9) or in other studies prescription of 300mg gabapentin 2 hours prior to lumbar disc surgery (10) and laparoscopic cholecystectomy (16) reduced pain after surgery. Although the exact mechanism of gabapentin in analgesia is still unknown, it has a tremendous desire to connect to the alpha2-delta subunits ofvoltage sensitive calcium channels, inhibiting calcium entry into neurons and reducing the release of excitatory neurotransmitters such as glutamate, substance P and nor-adrenaline (12, 17). It should be noted that these channels increase by damage caused by surgery in dorsal root ganglia and animal studies have shown that gabapentin, attaching to these channels can prevent allodynia and feeling too much pain (17, 18).

In contrast to the above studies, the results of a study by Adam et al, showed that in comparison to the control group prescription of 800mg gabapentin 2 hours before arthroscopic shoulder surgery under the interscalene nerve block cannotreducepost-operative pain (19). In another study, Brogly et al, concluded that using 1200mg gabapentin before thyroidectomy under cervical nerve block, has no effect on post-operative pain (20). In both these studies peripheral nerve blocks were used for surgery. A possible explanation could be that local blocks prevent the increased sensitivity in the posterior rami of spinal cord and dorsal root ganglia in response to surgical injury, and this may probably reduce the analgesic effect of gabapentin (19).

In the comparison between diclofenac and gabapentin, results of our study showed that these two drugs significantly reduce pain after dacryocystorhinostomy surgery at different times and there is no significant difference between them. In this regard, Yeganeh Moghadam et al. in their study compared the effect of diclofenac and gabapentin in the control of pain after tonsillectomy and came to the conclusion that these two drugs equally reduce pain at 2, 6 and 12 hours after tonsillectomy and there is no significant difference between their analgesic effects (21).

Studying the results of placebo group showed that Patients' pain after dacryocystorhinostomy progressively increases up to 2 hours and then it will be minimized. In this regard, Panah Khahi et al. in their study concluded that prescription of gabapentin before surgery can significantly reduce pain 2 hours after surgery. Moreover, in their study patients' need for the first dose of morphine in the gabapentin group had not decreased (8). These findings are consistent with our study. The peak blood concentration of gabapentin, is about three hours after its consumption (22). In our study gabapentin

consumption took place about 30 minutes before surgery and the average surgical time was about 40 minutes. It seems that the curve of the analgesic effect of gabapentin in our study is consistent with its blood concentration.

Conclusion

Both drugs gabapentin and diclofenac can decrease pain in the early hours after dacryocystorhinostomy. During the following hours, the patients' pain increase most probably because of decreases in drugs' blood levels (both anesthetics and pre-emptive analgesics).

Due to the decrease of gabapentin concentrations after 3 hours, it is suggested that higher doses of gabapentin in a single dose prior to surgery or multiple lower doses before and after surgery be used.

References:

1. Miller RD. Miller's Anesthesia. Philadelphia: Elsevier/Churchill Livingstone; 2005.
2. Dell R. A review of patient-controlled sedation. European journal of anaesthesiology. 1996;13(6):547-52.
3. Imani F, Safari S. "Pain Relief is an Essential Human Right", We Should be Concerned about It. Anesthesiology and pain medicine. 2011;1(2):55-7.
4. Shoar S, Esmaeili S, Safari S. Pain management after surgery: a brief review. Anesthesiology and pain medicine. 2012;1(3):184-6.
5. Kehlet H, Dahl JB. Are perioperative nonsteroidal anti-inflammatory drugs ulcerogenic in the short term? Drugs. 1992;44 Suppl 5:38-41.
6. Moote C. Efficacy of nonsteroidal anti-inflammatory drugs in the management of postoperative pain. Drugs. 1992;44 Suppl 5:14-29; discussion -30.
7. Maneuf YP, Gonzalez MI, Sutton KS, Chung FZ, Pinnock RD, Lee K. Cellular and molecular action of the putative GABA-mimetic, gabapentin. Cell Mol Life Sci. 2003;60(4):742-50.
8. Panah Khahi M, Yaghooti AA, Marashi SH, Nadjafi A. Effect of pre-emptive gabapentin on postoperative pain following lower extremity orthopaedic surgery under spinal anaesthesia. Singapore medical journal. 2011;52(12):879-82.
9. Turan A, White PF, Karamanlioglu B, Pamukcu Z. Premedication with gabapentin: the effect on tourniquet pain and quality of intravenous regional anesthesia. Anesthesia and analgesia. 2007;104(1):97-101.

10. Pandey CK, Sahay S, Gupta D, Ambesh SP, Singh RB, Raza M, et al. Preemptive gabapentin decreases postoperative pain after lumbar discoidectomy. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2004;51(10):986-9.
11. Gidal BE. New and emerging treatment options for neuropathic pain. Am J Manag Care. 2006;12(9 Suppl):S269-78.
12. Taylor CP, Gee NS, Su TZ, Kocsis JD, Welty DF, Brown JP, et al .A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy research. 1998;29(3):233-49.
13. Dahl JB, Mathiesen O, Moiniche S. 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in in the treatment of post-operative pain. Acta anaesthesiologica Scandinavica. 2004;48(9):1130-6.
14. Sills GJ. Not another gabapentin mechanism! Epilepsy currents / American Epilepsy Society. 2005;5(2):75-7.
15. Alimian M, Imani F, Hassani V, Rahimzadeh P ,Sharifian M, Safari S. Effects of single-dose pregabalin on postoperative pain in dacryocystorhinostomy surgery. Anesthesiology and pain medicine. 2012;2(2):72-6.
16. Pandey CK, Priye S, Singh S, Singh U, Singh RB, Singh PK. Preemptive use of gabapentinsignificantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2004;51(4):358-63.
17. Luo ZD, Calcutt NA, Higuera ES, Valder CR, Song YH, Svensson CI, et al. Injury type-specific calcium channel alpha 2 delta-1 subunit up-regulations in rat neuropathic pain models correlates with antiallodynic effects of gabapentin. J Pharmacol Exp Ther. 2002;303(3):1199-205.
18. Hurley RW, Chatterjea D, Rose Feng M, Taylor CP, Hammond DL. Gabapentin and pregabalin can interact synergistically with naproxen to produce antihyperalgesia. Anesthesiology. 2002;97(5):1263-73.
19. Adam F, Menigaux C, Sessler DI, Chauvin M. A single preoperative dose of gabapentin (800milligrams) does not augment postoperative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery. Anesthesia and analgesia. 2006;103(5):1278-82.
20. Brogly N, Wattier JM, Andrieu G, Peres D, Robin E, Kipnis E, et al. Gabapentin attenuates late but not early postoperative pain after thyroidectomy with superficial cervical plexus block. Anesthesia and analgesia. 2008;107(5):1720-5.

21. Yeganeh Mogadam A, Fazel MR, Parviz S. Comparison of analgesic effect between gabapentin and diclofenac on post-operative pain in patients undergoing tonsillectomy. Arch Trauma Res. 2012;1(3):108-11.

22. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clinical pharmacokinetics. 2010;49(10):661-9.

***Corresponding Author:**

Modir HE,

Arak, Valiye-asr Hospital, Anesthesiology and critical care Department, Iran.