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Pre-emptive Gabapentin versus Pregabalin for Acute Postoperative Pain after External Dacryocystorhinostomy Surgery under Regional Anesthesia: A Randomized Placebo-Controlled Trial

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ABSTRACT

Preoperative administration of gabapentin and pregabalin is proposed as a promising way of enhancing postoperative pain control. However there is a few studies about comparison of gabapentin with pregabalin. This study was designed to compare efficacy of pre-emptive gabapentin with pregabalin respecting to increase in duration of analgesia, reduction in total post-operative analgesic requirement and study side effects after external dacryocystorhinostomy (E-DCR). In a double blind randomized study, ninety patients undergoing E-DCR under regional anesthesia were randomly assigned in three groups to receive single dose oral 900mg gapapentin,300mg pregabalin or placebo 2 hours before the operation in the morning of the surgery. Pain was assessed by visual analog scale (VAS) until 24 hours after the operation time. Duration from the end of the surgery until analgesic (pethidine) administration and total pethidine requirement in the first 24 hours and side effects were recorded and the result of the three groups were compared. Patients in gabapentin and pregabalin groups had similar mean pain scores but lower than the placebo group during 24 hours after surgery (P=0/000).The total postoperative analgesic duration was 380±249.5 min in gabapentin group, 380±275.1 min in pregabalin group, whereas 208±91.7 min in placebo group (P=0.003).Total dose of analgesics in first 24 h was 21.66±12.27 mg in gabapentin group, 19.16±13.58 mg in pregabalin group and 48.5±17.07 mg in placebo group (P=0.000). Dizziness and somnolence were the only prominent side effects noticed in gabapentin and pregabalin groups, nousea frequency was higher in the placebo group than gabapentin and pregabalin groups(P<0.05). The study has shown that pre-emptive gabapentin and pregabalin 2h before E-DCR, both better than placebo, have been effective in reducing postoperative pain score, analgesic consumption and nausea/vomiting. Pergabalin and gabapentin and either can be used as a part of multimodal analgesia if not as sole analgesic.

Keywords: E-DCR, Postoperative pain, Analgesia, Gabapentin, Pregabalin

INTRODUCTION

"Excessive tearing due to obstruction of the nasolacrimal duct is a common ophthalmic problem. External dacryocystorhinostomy(E-DCR) is the procedure of choice designed to treat primary or secondary adult anatomical obstruction. Surgery produces injury with consequent release of histamine and inflammatory mediators. Noxious stimuli are transduced by peripheral nociceptors and transmitted by A and C fibers from peripheral visceral and somatic sites to the dorsal horn of the spinal cord and higher centers through the spinothalamic and spinoreticular tract, where they ultimately produce the perception of and affective component of pain" (Julius and Basbaum, 2001). "Central sensitization and hyperexcitability develop after the surgical incision and result in amplification of postoperative pain. Uncontrolled postoperative pain may produce a range of detrimental acute and chronic effects. These effects include sympathoadrenal hyperactivity, increased heart rate and blood pressure, increase

myocardial oxygen consumption, development of myocardial ischemia and infarction, development of hypercoagulability and deep venous thrombosis(DVT),delay return of postoperative gastrointestinal motility and paralytic ileus, insufficient depth of breathing and atelectasis" (Robert, 2010).Preventing the establishment of altered central processing by analgesic treatment may result in short-term(e.g.,reduction in postoperative pain and accelerated recovery) and long-term(e.g.,reduction in chronic pain and improvement in health-related quality of life[HRQL]) benefits during a patient's convalescence (Carli et al ., 2002). Although at the present time opioid analgesics are one of the cornerstone options for the treatment of postoperative pain ,because of the known side effects of these drugs, a lot of efforts are made to reduce the need for opioid doses in relieving pain after operation by administering other drugs or practicing other methods including multimodal analgesia and pre-emptive analgesia (Imani and Safari, 2011; Kelly et al ., 2001; Ong et al., 2005; Shoar et al., 2012; Dell et al., 1996). E-DCR is among the surgeries that cause mild to moderate pain and administering opioids to relieve this level of postoperative pain leads to respiratory side effects, nausea, vomiting, excessive sedation, pruritus, and urinary retention especially in old age, therefore utilizing other drugs instead of opioids can be an appropriate and practical solution in controlling the patient's pain. Considering the fact that nonsteroidal anti-inflammatory drugs(NSAIDs) are administered to provide effective analgesia for mild to moderate pain after eye surgeries and these drugs have a number of side effects, including decreased hemostasis, renal dysfunction, gastrointestinal hemorrhage, It seems that administering other drugs that act on different analgesic mechanisms to alleviate patient's pain seems logical (Kehlet and Dahl, 1992; Moote, 1992; Dabbagh, 2011; Dahle et al., 2004; Kong and Irwin, 2007). Preoperative administration of anticonvulsive agent, that is gabapentin and its successor pregabalin, is proposed to be a promising way of enhancing postoperative pain control (Kissin, 2005; Bornemman et al., 2010; Zhang et al., 2011; Ledere et al., 2011). Gabapentin is a structural analogue of gamma amino butyric acid (GABA), which was initially introduced in 1994 as an antiepileptic drug (AED), particularly for partial seizures. It has a high binding affinity for the 2subunit of the presynapthic voltage-gate calcium channels which inhibits calcium influx and subsequent release of excitatory neurotransmitters in the pain pathways (Jianren et al., 2009). Gabapentin has an analgesic and opioid-sparing effect in acute postoperative pain management (Mathiesen et al., 2007) and significant reductions in postoperative analgesic requirements 24 hours after surgery were found in six studies [abdominal hysterectomy, spinal surgery,vaginal hysterectomy, radical mastectomy and laparoscopic cholecystectomy] (Turan et al., 2004a,b; Pendy et al., 2004; Rorarius et al., 2004; Dierking et al., 2004; Fassoulaki and Patris, 2002; Driks et al., 2002). Pregabalin is a potent and more effective analogue of gabapentin and acts as a better ligand for α2-δ protein subunit than gabapentin and reduces the release of several excitatory neurotransmitters and blocks the development of hyperalgesia and central sensitization. Pregabalin has an amino acid substitution at third position, which allows increased lipid solubility and diffusion across blood brain barrier and fewer drug interactions due to the absence of hepatic metabolism. The pharmacological and pharmacokinetic profiles of pregabalin provide a predictable basis for its use in clinical practice (Ben-Menachem, 2004; Shenker and MacAuley, 2005; Guay, 2005; Bockbrader et al., 2000). There are initial studies showing some evidence that it may have efficacy in acute pain similar to that of gabapentin (Hill et al., 2001; Paech et al., 2007; Jokela et al., 2008a,b; Mathiesen et al., 2008; Hurely et al., 2002). To the best of our knowledge, there are no trials comparing pre-emptive pregabalin with gabapentin in postoperative pain in the available literature. Therefore, this research has been carried out with the aim of studying the postoperative analgesic benefit in patients administered a single dose of oral gabapentin or pregabalin as premedication (in the morning of the surgery) for E-DCR under regional anesthesia and to compare their postoperative efficacy with respect to their effects on postoperative pain scores, increase in duration of analgesia, reduction in total post-operative consumption of analgesics and study side effects and complications.

PATIENTS AND METHODS

The study was randomized, double blind and placebo controlled. After approval of medical university ethics committee and obtaining informed consent from all the patients, ninety patients scheduled for E-DCR under regional anesthesia, hospitalized in the Velayat university hospital from September 2011 to

December 2012.Inclusion criteria consisted of an age limit of 20 - 80 years, ASA (American Society of Anesthesiologists) physical status of I to II and presenting a written consent to take part in the study. Patients with known hypersensitivity to gabapentinoids, history of seizure, positive history of gabapentin or pregabalin consumption, psychiatric disorders, drug abuse, known liver or renal disease, chronic pain syndroms, and the patients who had an intake of analgesic drugs 24 hours before the test were excluded from the study. The patients were randomly assigned into three groups of 30 by a table of random numbers. Patients in gabapentin group received single dose of gabapentin 900mg, and in pregabalin group were administered pregabalin 300mg, while the patients in the placebo group received placebo capsule. All doses of pregabalin, gabapentin and placebo capsule were given orally 2 hour prior to entering the operating room in the morning of the surgery day. No other sedative premedication was instituted. Patients were acquainted with the utilization of a 10-cm linear visual analog scale (VAS) for pain, where 0 donate "no pain" and 10 donate"worst imaginable pain", the evening before surgery. Routine monitoring, in the form of non invasive blood pressure(NIBP), pulse oximetry(SpO2) and electrocardiogram(ECG) was instituted on arrival in operating room. After establishing intravenous line, midazolam 1-2mg was injected as premedication. As local anesthesia solution, a mixture of 2% lidocaine, 0.5% bupivacaine and 1:100,000 adrenaline was prepared and injected into the incision site and by entering the needle through the caruncle over the posterior lacrimal crest and anterior ethmoidal nerve. In order of having a good nasal mucosal shrinkage and after spraying the nasal space with lignocaine nasal spray, two applicators were soaked into a 0.1% adrenaline solution and positioned high in the nasal space, anterior to the middle turbinate on the side to be operated. For all cases a standard external DCR performed by a single plastic eye surgeon. At the end of surgery all the patients were transferred to post anesthesia care unit (P.A.C.U) and pain was assessed postoperatively by visual analog scale(VAS) immediate postoperatively and,1 hour, 2hours,4 hours,8 hours,12 hours,18 hours, 24 hours thereafter, which was explained to the patient during preoperative visit. Blinding was done during follow up in ward, once patient was shifted to the ward; another anesthetist unaware of patient's group was responsible for charting the pain score by VAS scale. Any patient with VAS score of more than three, were administered pethidine 0.5 mg/kg intravenously and documented. Time since the end of surgery until the first injection of analgesic and total dose of analgesic in first 24 hours was recorded. Any complication like dizziness, somnolence, diplopia, vomiting, confusion, pain and urinary retention were recorded in the first 24 hours post- operative period.

Statistical Analysis

Sample size was estimated in consultation with statistician. Thirty was the smallest number in each group, where any results could be statistically significant hence this number was selected. At the end of the study, the data gathered from the study were analyzed using statistical analysis software SPSS 14.0(SPSS Inc. Chicago, IL, USA). One-Way analysis of variance (ANOVA) was used for comparison of total analgesic consumption over 24 hours and the time intervals to first analgesic, whereas Tukey's Honestly Significant Difference (HSD) was used for multiple comparisons. The incidence of side effects such as nausea was compared using the chi squared test for multiple variables. Data was reported as mean value ±S.D. A P-value of < 0.05 was considered statistically significant.

RESULTS

Ninety patients, thirty in each group were included in the study and analyzed. According to the Table-1 the three groups are similar in demographic characteristics like age, weight, sex, A.S.A physical status, duration of surgery, background disease and there is no statistically significant difference between the three groups ($P>0.05$). Postoperatively, mean pain scores (VAS score) were significantly higher in the control group (3.38±0.38) than in the gabapentin (2.47±0.38) and pregabalin (2.2±0.42) groups ($P=0.000$), but the difference between the gabapentin and pregabalin groups were statistically non significant ($P >0.05$). The mean total postoperative analgesic duration (time to first postoperative analgesic request) was longer in the gabapentin and pregabalin groups versus control group; as it was (382 ±249.5 min) for gabapentin group,(380± 275.1min) for pregabalin group, while in control group it

was (208.6 ±91.7 min) (P=0.003) (Table 2). The mean total dose of analgesic (pethidine) consumption in first 24h was significantly decreased in the gabapentin (21.66±12.27 mg) and pregabalin (19.16±13.58 mg) groups versus control group (48.5±17.07 mg) (P=0.000), and the difference between the gabapentin and pregabalin groups were statistically non significant (P>0.05) (Table 2). There was no significant difference in the incidence of side effects between gabapentin and pregabalin groups. The incidence of somnolence was 22% in gabapentin group, 19% in pregabalin group and 16% in control group (p>0.05) (Figure 2). The incidence of dizziness was 19% in gabapentin group, 16% in pregabalin group and 6% in control group (P<0.05) (Figure 2). Nausea frequency was 16% in the gabapentin group, 13% in pregabalin group and 39% in the placebo group which is statistically significant (P = 0.003) (Figure 2). Vomiting frequency of the gabapentin group was 13% (four patient), pregabalin group was 9% (three patients) and in the placebo group was 26% (eight patients) (P<0.05) (Figure 2). There were no significant between group differences in the incidence of pruritus (Figure 2). None of the patients complained about other side effects such as: peripheral edema, sedation, headache or visionary disorder in this study.

Table1. Demographic Characteristics of the patients

	Gabapentin	Pregabalin	Placebo	P.Value
Age(y)mean±SD	69.23±12.02	65.56±16.68	66.33±15.47	0.608
Weight(kg)mean±SD	64.63±6.6	64.5±5.02	65.43±6.27	0.810
Sex, male/female ratio	16/14	14/16	16/14	0.839
ASA Class,I/II ratio	8/22	9/21	10/20	0/499
Duration of Surgery	57.6±6.26(min)	58.7±5.02(min)	58±5.01(min)	0.856

Table2. Data regarding Pain Score, requirement for postoperative analgesic

	Gabapentin	Pregabalin	Placebo	P.Value
VAS in 24h,mean±SD	2.47±0.38	2.2±0.42	3.38±0.38	0.000
Time to 1st dose of pethidine(min),mean±SD	382±249.5	380±275.1	208.06±91.7	0.003
Required dose of pethidine(mg),mean±SD	21.66±12.27	19.16±13.58	48.5±17.07	0.000

DISCUSSION

Uncontrolled postoperative pain may produce a range of detrimental acute and chronic effects. The attenuation of perioperative pathophysiology that occurs during surgery through reduction of nociceptive input to the CNS and optimization of perioperative analgesia may decrease complications and facilitate recovery during the immediate postoperative period and after discharge from the hospital (Robert, 2010). Pre-emptive Analgesia(Definitions of preemptive analgesia include what is administered before the surgical incision, what prevents the establishment of central sensitization resulting from incisional injury) has been shown to be more effective in control of postoperative pain by protecting the central nervous system from deleterious effect of noxious stimuli and resulting allodynia, and hyperalgesia (Kissin, 2005). In recent years several studies have reported the usefulness of gabapentin and pregabalin in perioperative setting resulting in reduced postoperative pain intensity, postoperative analgesic consumption, opioid- related adverse effects and patient satisfacation (Shneker et al., 2005; Rorarius et al., 2004; Al-Mujadi et al., 2006; Turan et al., 2006). Conclusions about the optimal dose and duration of the treatment cannot be made because of the heterogeneity of the trials. Studies are needed to determine the long-term benefits, if any, of perioperative gabapentinoids (Tiippana et al., 2007).The present study reveals that gabapentin 900mg and pregabalin 300mg, given orally 2 hours before external

dacryocystorhinostomy (E-DCR) resulted in significantly reduction in postoperative analgesic consumption compared with placebo. Gabapentin has been used preoperatively in varying dosages from 300 to 1200 mg, but 1200 mg has been the common, single highest safe dose used in previous trials on postoperative pain (Turan et al., 2004; Rorarius et al., 2004; Driks et al., 2002; Ho et al., 2006). In one RCT, increasing the dose from 300 mg to 600–1200 mg improved the analgesic and opioid sparing effect of gabapentin, but there were no significant differences between the effects of the higher doses (Pandy et al., 2005). In a study by Rimaz and colleagues showed a single preoperative oral dose of 1200mg gabapentin resulted in a substantial reduction in postoperative morphine consumption and pain scores after surgical debridement in burn patients (Rimaz et al., 2012). Our purpose of choosing 900mg was also to find whether a dose below the already tested dose of 1200mg could be equally efficacious at the cost of fewer side effects. Hill *et al.* found 300 mg pregabalin to be more effective than 50 mg pregabalin or 400 mg ibuprofen in attenuating pain after dental extraction (Hill et al., 2001). Paech *et al.* did not observe improvement in analgesia with a single preoperative dose of 100 mg pregabalin before minor gynecological surgery involving uterus and cervix (Paech et al., 2007). Also, Jokela *et al.* reported that premedication with pregabalin 150 mg in day-case gynecological laparoscopic surgery did not reduce fentanyl consumption (Jokela et al., 2008). Alimian et al. examed the efficacy of 300mg pregabalin in alleviating the postoperative pain of dacryocystorhinostomy (DCR) surgery and concluded a single 300mg dose of pregabalin,1 hours before DCR can effectively reduce pain intensity and also reduce opioid dose and nausea/vomiting(Alimian et al., 2012). One systematic review carried out by Zhang and his colleagues collected all reliable clinical trials to investigate the efficacy of pregabalin in alleviating postoperative pain,this meta-analysis showed that administering Pregabalin in doses less than 300 mg before the operation cannot significantly alleviate the pain in the first 24-hour period after the surgery while increasing the dose can significantly decrease the pain intensity and amplify the side effects resulting from pregabalin(Zhang et al., 2011). Since the doses of 100 and 150 mg were ineffective in day case surgeries, a higher dose (300mg) of pregabalin was considered in our study for external dacryocystorhinostomy (E-DCR) surgery on the basis of previous studies (Hill et al., 2001; Alimian et al., 2012; Mathiesen et al., 2008; Tiippana et al., 2007). Their administration 2 hours prior to surgery appeared rational in order to achieve maximum plasma concentration at the time of surgical stimuli though pregabalin is rapidly absorbed (peak: within 30 minutes to 2 hours) and gabapentin is slowly absorbed (peak: 2 hours). Pain scores were decreased with a single preoperative dose of gabapentin and pregabalin in the 24h postoperative period in our study (Figure 1) which is consistent with previous studies (Tiippana et al., 2007; Dahl et al., 2004). Time to first request for analgesia was longest in pregabalin group which could be explained due to its quicker onset of action than gabapentin. In our study the incidence of nausea and vomiting was higher in control group than gabapentin and pregabalin groups that were similar to earlier studies (Tiippana et al., 2007; Dahl et al., 2004). The increased nausea and vomiting observed in the control group could be due to more pethidine consumption. Dizziness and somnolence were the two most common side effects associated with gabapentin and pregabalin groups. The incidence reported in present study was similar to earlier studies (Rorarius et al., 2004; Al-Mujadi et al., 2006; Turan et al., 2006). Limitations in our study were administration of these drugs in a single dose, the half-life of these drugs is 5-7 hours, which may have resulted in decreased effect over time and conclusion about the optimal dose and duration of the treatment cannot be made.

In conclusion, preoperative gabapentin and pregabalin are effective than placebo in reducing pain intensity, opioid consumption and opioid-related adverse effects after surgery. Gabapentin and pregabalin have very few adverse effects of their own. Because of the heterogeneous data of these studies, no conclusions about the optimal dose and duration of the treatment can be drawn. The efficacy of gabapentinoids in preventing chronic pain needs to be elucidated in future studies.

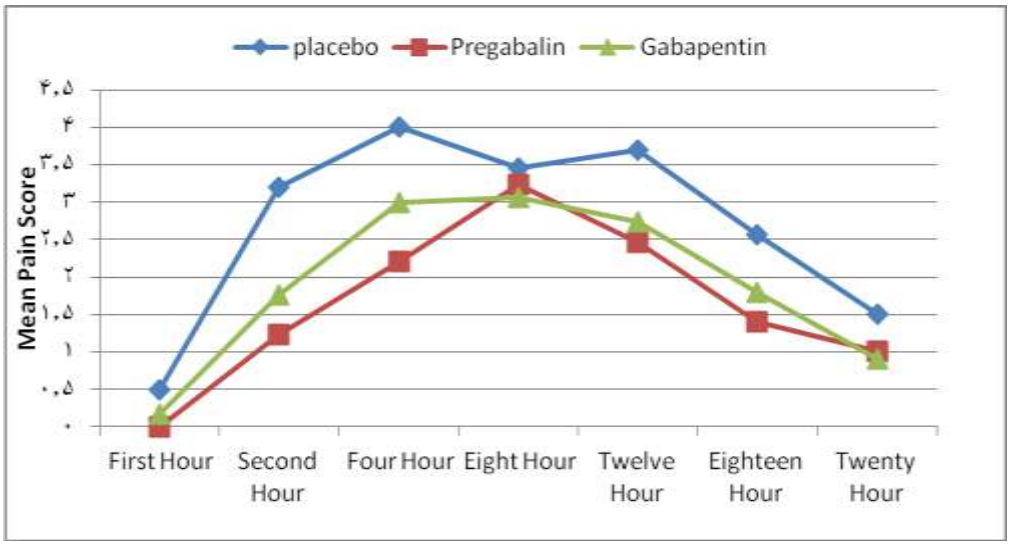

Figure 1: Visual Analogue Score over the 24 hour postoperative period. Gabapentin and pregabalin Groups experienced least amount of pain during time interval. Data is expressed as mean±SD, Placebo VS Gabapentin & Pregabalin (P=0.000), Gabapentin VS Pregabalin (P>0.05)

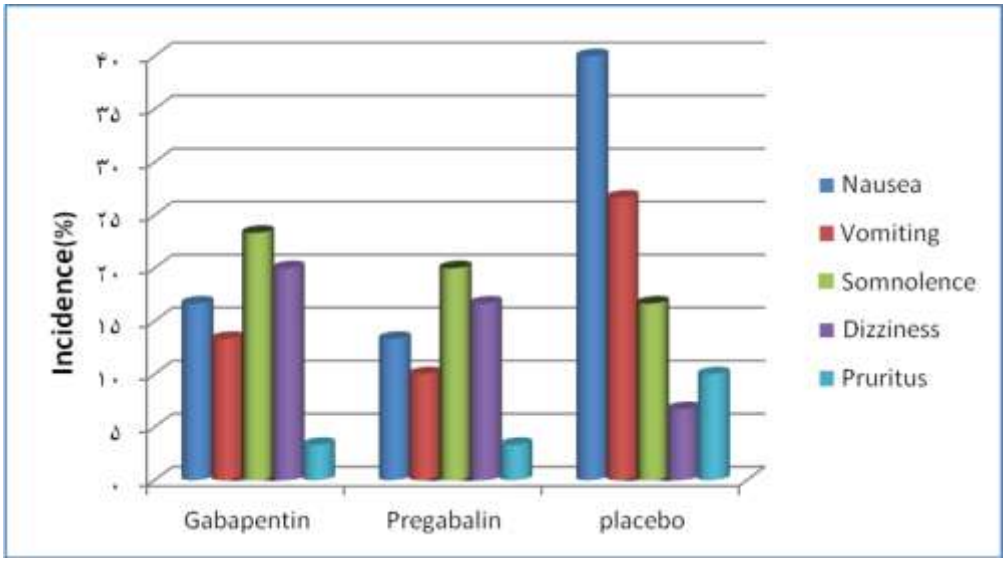

Figure 2: Incidence of side-effects, patients in gabapentin and pregabalin groups had lower Incidence of postoperative nausea and vomiting than placebo group (P<0.001), Dizziness Was more common in Gabapentin & Pregabalin groups than Placebo group (P<0.05).

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