EFFECT OF SINGLE-DOSE PREGABALIN ON POSTOPERATIVE PAIN IN DACRYOCYSTORHINOSTOMY SURGERY

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ABSTRACT

Objective: To evaluate the analgesic potential of pregabalin in ambulatory dacryocystorhinostomy surgeries under general anaesthesia.

Study Design: Quasi-experimental study.

Place and Duration of Study: Tertiary Care Hospital Rawalpindi, from Nov 2019 to Sep 2020.

Methodology: A total of 110 patients undergoing ambulatory dacryocystorhinostomy surgery at our hospital were included in the study. Participants were divided into two groups, group A (n=55) were administered 150 mg oral pregabalin, while a placebo was given to participants of group B (n=55). Post-operative pain was assessed at recovery, four and eight hours after surgery with the help of the visual analogue scale.

Results: Mean age of participants was 43.05 ± 7.5 years. Gender wise distribution showed 62 (56.4%) males and 48 (43.6%) females. At recovery, four and eight hours after surgery the mean pain scores in group A (pregabalin) vs group B (placebo) were (2.98 ± 0.8 vs 4.98 ± 0.8, p<0.001, 2.67 ± 0.6 vs 5.02 ± 0.8, p<0.001 and 1.49 ± 2.9 vs 2.95 ± 0.8, p<0.001 respectively). Opioid administration frequency in trial versus placebo group was [11 (20%) vs 32 (58.2%), p<0.001].

Conclusion: Pregabalin has analgesic potential moreover decreased postoperative consumption of opioids and associated adverse effects such as nausea and vomiting. Hence making it a suitable agent for pain relief in ambulatory surgeries.

Keywords: Opioids, Pregabalin, Visual analogue scale.

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INTRODUCTION

Pain management is still of prime concern in surgical patients, despite all endeavours a definitive analgesic, with negligible adverse impacts is yet to be explored for intense post-operative pain[1]. Postoperative pain is a source of patient discomfort and dissatisfaction, leading to various fundamental adverse impacts. Therefore, render an early post-operative recovery process which is desirable in ambulatory surgeries in particular. Early recovery protocols and daycare surgeries are of emerging concern due to constrained accessibility of healthcare assets with increased population in underdeveloped countries, adding to struggle for the arrangement of safe quality consideration[2,3].

Distressing effects due to failure of pain alleviation incorporate adrenal sympathetic surge, ischemic changes, tachycardia, inadequate respiratory effort, atelectasis, and elevated mean arterial pressure[4]. Conventional practices are to utilize narcotics judiciously for postoperative pain relief however higher adverse impact profile of narcotics prompted endeavours and search for opioid-sparing multimodal analgesia without compromising patient safety. Financial compatibility and adequate safety profile regimes are desired traits[5].

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently recruited as rescue agents in ophthalmological surgeries as the greater part of the procedures are proceeded as daycare. Reportedly, pain pervasiveness can be as high as 98% within the early hours of the postoperative period. However, considering greater part of ocular patients are geriatric population and the pernicious impacts of NSAIDs on the renal and digestive system restricts its utility[6].

Pregabalin is anticonvulsant, pain-relieving properties of which are being investigated strenuously. It acts by reduction of calcium entry via nerve terminals of the central nervous system where it lowers pain mediators substance P, glutamate and noradrenaline. Pregabalin is frequently employed in neuropathic, tissue and inflammatory pain, moreover, fibromyalgia and chronic pains demonstrate its efficacy as a pain relief agent. It has low adverse effects profile and

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provides the advantage of anxiolytic as well which is an alluring preoperative effect[7].

Recent breakthroughs in Anaesthesia and Surgical strategies, alongside heightened financial burden, have brought about an escalating number of surgeries being performed on a day case premise globally. Day case Surgical procedures account for 60-70% of the total number in North America around the 1990s, however, represent a diminished rate around the world therefore efforts are in hand to augment numbers[8]. Day case patients represent minimal surgical trauma hence their dispense primarily depends on anaesthetic recuperation. Dacryocystorhinostomy (DCR) is a surgical procedure that presents patients to mild to moderate post-operative pain hence excessive opioid administration to the patient will expose them to a number of adverse reactions, for example, nausea, vomiting, respiratory depression and urinary retention. Most of the subject procedures performed as day cases are therefore dependent on Four 'A's: "Alertness, Alimentation, Analgesia & Ambulation"[9].

Respiratory depression, nausea, vomiting or pain will defer the accomplishment of post anaesthetic discharge scoring system (PADSS) Score of the patient, therefore discharge from the Postanesthesia care unit. Old age and eye procedures already have an increased propensity for nausea, and vomiting therefore opioid administration is not persuading further. Consequently demonstrated that the use of multi-modal analgesia modalities, in particular, is helpful[10].

We speculated that Pregabalin, when utilized as an assistant to acetaminophen in ambulatory ophthalmological surgical procedures, will ease the pain with less narcotic utilization and associated adverse impacts, such as nausea and vomiting.

METHODOLOGY

The quasi-experimental study was conducted at Tertiary Care Hospital, Rawalpindi, from November 2019 to September 2020, approval taken from the ethics research committee of the hospital (228/ERC).

The sample size was calculated using WHO online calculator, for a two-tailed hypothesis, 80% study power, 95% confidence level, the effect size of 1.26[11,12], and a pooled standard deviation of 1.5. The minimum required sample size was calculated to be 48 (24 in each group).

Inclusion Criteria

Total 110 consecutive patients fulfilling the inclusion criteria, undergoing Endoscopic DCR surgery under general anaesthesia from both genders with age group between 18-55 years were included. ASA status I or II, minimal anticipated intraoperative blood loss, least expectation of intraoperative or postoperative complications, surgical duration of up to 120 minutes were included.

Exclusion Criteria

While patients who denied consent, or had a body mass index of >30, were pregnant and/or lactating females, having a systemic illness such as hypertension, diabetes mellitus, difficult airway, surgery duration greater than two hours and those allergic to pregabalin were excluded from enrollment in the study.

Postoperatively pain was evaluated with a visual analogue scale (VAS).VAS is a psychometric response scale for the estimation and pain perception of patients that cannot be estimated directly. In this scale, subjects react to their degree of pain by demonstrating intensity on a continuous line between two endpoints (Figure)[11].

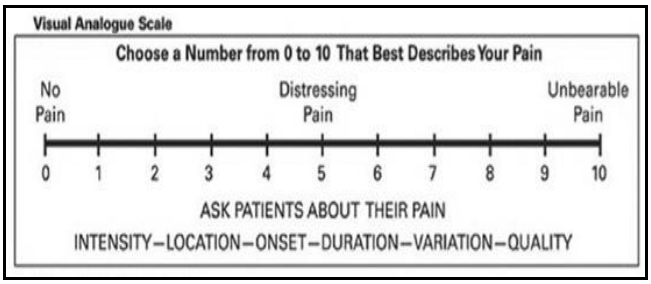

Figure: Visual analogue scale.

As per study protocol, all the patients were interviewed, briefed, counselled about the procedure and informed written consent was taken. Before reporting to the operation theatre, a detailed pre-anaesthesia assessment was carried out in all patients with necessary laboratory evaluation parameters to adhere to our inclusion and exclusion criteria, besides, to ensure patient safety which is of utmost concern in anaesthetic management. As pre-operative preparation consummation of fundamental documentation and an overnight fast/nil per oral was ensured. Study participants were equally divided into two groups, one group was assigned to treatment drug while others to a placebo pill. Two hours before the start of surgery, participants of group A (n=55) were administered 150 mg tablet pregabalin stat dose with a sip of water, while placebo pill was given to participants of group B (n=55).

On the day of surgery, patients were brought to operation theatre and before initiating general anaesthesia standard monitoring such as blood pressure (non-invasive method), pulse oximeter (SpO2), end-

tidal carbon dioxide (ETCO2) and electrocardiography electrodes attached. 18G IV cannula passed under aseptic conditions. All the patients were premedicated with intravenous injections of paracetamol 15mg/kg, dexamethasone 0.08mg/kg, metoclopramide 0.1mg/kg and Midazolam 0.07-0.15mg/kg. Patients were Pre oxygenated with 100% oxygen for 3 minutes. Induction was done with intravenous injection of propofol at a dose of 2mg/kg. Muscle relaxation was achieved with 0.5 mg/kg of intravenous injection atracurium followed by laryngoscopy and intubation by a qualified anaesthetist after 3 minutes. Posterior pack placed with Magill with laryngoscopy under vision to prevent aspiration in surgeries where it was anticipated. Maintenance of general anaesthesia ensured with inhalational anaesthetic isoflurane at 1.5 minimum alveolar concentration and injection atracurium 0.1mg/kg. At the end of the surgery, the muscle relaxant was antagonized by intravenous Neostigmine and Glycopyrrolate.

Patients were kept in post anaesthesia recovery unit for 1 hour and later moved to the post-operation ward guaranteeing stable imperative signs and meeting recuperation scores, well inside the premises of the operation theatre. Pain scores were analyzed with a visual analogue scale immediately in the recovery area, 4 hours and 8 hours postoperatively. Patients with a complaint of severe pain >8 hours were admitted to inpatient facility thus rejected out of preliminary. Injection Nalbuphine in a dose of 0.1mg/kg body weight was given in stat dose to those patients with complaint severe pain or visual analogue score of ≥5. Frequency of nausea and vomiting recorded postoperatively.

Variables evaluated age, gender, American Society of Anesthesiologists status (ASA), nausea, vomiting, analgesic requirements and visual analogue score [at recovery, fourth and eighth hour].

Data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 22. Descriptive statistics of continuous variables including age and visual analogue scores were expressed as mean and standard deviation, while categorical variables including gender, opioid consumption, nausea, vomiting and American Society of Anesthesiologists status, were expressed as frequency and percentages. The mean value of the primary outcome of the study i.e. post-operative pain, measured on a continuous scale, was compared between two study groups using student's t-test. Other categorical variables were compared using the chi-square test. The *p*-values ≤0.05 was considered to be statistically significant.

RESULTS

A total of 10 patients were enrolled in the study, who were equally divided into two groups, group A (n=55) received study drug pregabalin while group B received a placebo pill. The mean age of 110 study participants was 43.05 ± 7.5 years and there were 62 (56.4%) males while 48 (43.6%) females were in the study group. Out of 110, 31 (28.2%) belonged to the American Society of Anesthesiologists (ASA) class I, while 77 (70%) and 2 (1.2%) belonged to class II and III respectively.

Among group A, the mean age of patients was 42.73 ± 8.8 years, with 29 (52.7%) males and 26 (47.3%) females. There were 15 (27.3%) patients in group A with American Society of Anesthesiologists physical status classification I and 39 (70.9%) patients with class II classification. Whereas in group B, the mean age of patients was 43.38 ± 6.02 years, with 33 (60%) and 22 (40%) males and females respectively. There were 16 (29.1%) and 38 (69.1%) belonging to the American Society of Anesthesiologists physical status classification I, II and III respectively. Both the study groups were comparable at baseline, with insignificant differences between age, gender and physical status classification (*p*=0.650, *p*=0.442 and *p*=0.978 respectively), as shown in Table-I.

Table-I: Summary of baseline characteristics among study groups.

Baseline Characteristics	Study Groups		*p*-value
	Group A Pergabalin (n=55)	Group B Placebo (n=55)	
Age (years)			
Mean ± SD	42.73 ± 8.8	43.38 ± 6.0	0.650a
Gender, n (%)			
Male	29 (52.7%)	33 (60%)	0.442b
Female	26 (47.3%)	22 (40%)	
American Society of Anaesthesiologist Status			
I	16 (29.1%)	17 (30.9%)	0.978b
II	39 (70.9%)	38 (69.1%)	

Post-operative pain was appraised immediately after surgery, followed by 4 and 8 hours after surgery for both the study groups with the help of the Visual Analogue Scale. At recovery time, it was found that the mean pain score for patients belonging to Pergabalin group A was significantly lower as compared to placebo group B (2.98 ± 0.8 vs 4.98 ± 0.8, *p*<0.001). Similarly, at 4 and 8 hours after surgery, again the mean pain score was significantly lower in group A as compared to group B (2.67 ± 0.6 vs 5.02 ± 0.8, *p*<0.001 and 1.49 ± 2.9 vs 2.95 ± 0.8, *p*<0.001 respectively) as shown in the Table-II.

Table-II: Comparison of postoperative pain between group A and B.

Post-Operative Pain	Study Groups		*p*-value
	Group A Pergabalin (n=55)	Group B Placebo (n=55)	
Mean Visual Analogue Scale score at recovery time (Mean ± SD)	2.98 ± 0.8	4.98 ± 0.8	<0.001
Mean Visual Analogue Scale score 4 hours after surgery (Mean ± SD)	2.67 ± 0.6	5.02 ± 0.8	<0.001
Mean Visual Analogue Scale score 8 hours after surgery (Mean ± SD)	1.49 ± 2.9	2.95 ± 0.8	<0.001

Table-III: Comparison of postoperative opioid consumption for relieving pain between pergabalin and placebo group.

Opioid Consumption	Study Groups		*p*-value
	Group A Pergabalin (n=55)	Group B Placebo (n=55)	
Yes	11 (20%)	32 (58.2%)	<0.001
No	44 (80%)	23 (41.8%)	

Table-IV: Frequency of nausea and vomiting among two study groups.

Adverse Effects	Study Groups		*p*-value
	Group A Pergabalin (n=55)	Group B Placebo (n=55)	
Nausea	6 (10.9%)	25 (45.5%)	<0.001
Vomiting	3 (5.5%)	8 (14.5%)	0.112

Opioid consumption for analgesic effects is a common practice among surgery patients to relieve post-operative pain irresponsive to other analgesic drugs. In terms of opioid consumption, it was observed that a significantly lesser number of patients belonging to group A required opioids for pain relief as compared to group B [11 (20%) vs 32 (58.2%), p<0.001] as shown in the Table-III. About the incidence of side effects among study groups, it was observed that 6 (10.9%) patients in group A experienced nausea while 25 (45.5%) in group B, and the difference was significant with a p-value of <0.001. However, there was no significant difference observed in terms of vomiting among patients belonging to group A and group B [3 (5.5%) vs 8 (14.5%), p=0.112] as shown in Table-IV.

DISCUSSION

Pregabalin had been explored for alleviation of intense post-surgical pain. According to study outcomes, Pregabalin is useful in the reduction of postoperative narcotic consumption with significant pain-relieving potential. Since endoscopic dacryocystorhinostomy is a minimally invasive procedure, therefore, can easily be performed as daycare surgery. Incautious utilization of opioids as analgesics can postpone patient discharge because of related deleterious effects, for example, nausea, vomiting and urinary retention etc which are pronounced in extremes of age. Moreover, opioid administration requires close monitoring for a longer duration. Numerous studies in various specialities had been carried out to prove the efficacy of pregabalin as an effective adjunct in pain management practices, findings well versed with our results.

Alimian *et al* conducted a double-blinded, randomized clinical preliminary on dacryocy storhinostomy patients. The patients were divided into two groups of Pregabalin (300mg) and Placebo, an hour before the procedure. Pain severity (VAS) was recorded until 24 hours after the surgery furthermore the administration of narcotics and nausea or vomiting was endorsed during the initial 24-hour post-surgery. Postoperative pain in the pregabalin group at recovery was essentially lower than placebo (p=0.001), results are therefore adherent to our analysis although we employed a lower dose of trial drug. In the pregabalin group (17.5%) of the patients got narcotics while in the placebo group the figure was 52.5% (p=0.001) however in our study (20%) patients were in the drug group whereas (58.2%) in the placebo group were administered opioids. Nausea prevalence was additionally higher in the placebo batch than the pregabalin batch (p=0.003), results accordant to study[12].

Akdogan *et al*, evaluated pain severity with visual analogue scores in patients who underwent Total Knee Arthroplasty at 4th, 12th and 48th hours where patients were given tramadol as regulated by patient pain perception, which ended up significantly lower in the pregabalin batch. A sum of 126 patients was included in the study. Sixty-five (51.6%) were administered 150 mg pregabalin 2 hours before the surgery (pregabalin group) and 61 (48.4%) were not given pregabalin (non-pregabalin group), The mean reduction in VAS scores from the fourth hour to the 48th hour was (7.69%) in the pregabalin group and (5.6%) in the non-pregabalin group. Nausea was endorsed in 18 (27.7%) in pregabalin group while in 24 (39.3%) in the placebo group (p-value=166)[13].

Kheirabadi *et al* considered postoperative analgesic management in the orthopaedic surgical procedure of the lower extremity. Groups got 300mg oral gaba-

pentin, 75mg oral pregabalin, 200mg oral celecoxib, and starch as placebo. The intensity of postoperative pain (utilizing visual analogue scale), mean blood pressure, opioid utilization and adverse impacts were recorded every 60 min and later every 6 hourly. Significant decrease in pain severity was recorded among the pregabalin group with visual analogue scores recorded as Placebo 4.83 ± 1.78, Gabapentin 3.83 ± 2.90, Pregabalin 2.65 ± 2.65 and Celecoxib 3.25 ± 2.38 (*p*-value 0.014)[14].

Mansor *et al* studied the impacts of pregabalin as pre-emptive analgesia in mastectomy and concluded that 150 mg pregabalin before surgical procedure provides favourable outcomes. Forty-nine patients ASA I or II, ranged between 20-60 years, planned for a mastectomy were enlisted, randomized into two batches placebo (n=24) or pregabalin (n=25). Before being called to operation theatre patients were administered either oral pregabalin 150 mg or placebo. The evaluation of pain score was performed at recovery, 2, 4, 6 and 24 hours postoperatively with the verbal numeral rating score (VNRS).VNRS scores for pain lower in the pregabalin batch at 2 hours (*p*-value 0.024), 4 hours (*p*-value 0.006) and 6 hours (*p*-value 0.003) postoperatively[15].

Ahn *et al* conducted a randomized controlled trial for analgesic efficacy of 150mg pregabalin in arthroscopic shoulder surgeries given preemptively to patients before surgery. To assess pain intensity they used a numeric rating score for pain (0–10). They concluded statistically significant lower scores in the pregabalin group. As per their results at 06 hours (1.8-4.0), 24 hours (1.9-3.8) and 48 hours (0.6-2.3) with a 95% confidence interval. They proved pregabalin superior in terms of opioid-sparing effect however adverse effects profile (nausea, vomiting, dizziness) was similar which is contradictory to study results as the pregabalin group displayed promising results in terms of nausea [$p<0.001$] whereas insignificant concerning vomiting [$p0.11$] but still lower frequency of (5.5%) when compared with (14.5%) of placebo[16].

Gaber *et al* designed a pain relief regime for thoracotomy, they administered 150 mg one hour before surgery, 12 hours after surgery and twice daily for 5 days. Pain intensity was assessed with a visual analogue score.Visual Analogue Scores assessed at 0, 6, 12, 18, 24 hours thus yielded results of 2.9 ± 0.7,3.3 ± 0.9, 2.6 ± 0.8,2.1 ± 0.6 and 1.6 ± 0.6 respectively. The pregabalin group displayed a significant reduction in morphine consumption and neuropathic pain[17].

Bouzia *et al* performed a double-blinded prospective study on cardiac surgery patients by assigning a placebo. 75mg oral and 150mg oral pregabalin to each group. Recorded results at 8 hours, 24 hours and 3 months. The pregabalin group displayed a statistically significant lower morphine consumption rate (*p*-value–0.001). Patients getting pregabalin required fewer morphine boluses (10 in controls versus 6 in group 1 versus 4 in group 2). The number of patients with insomnia or analgesics demand was lower in the pregabalin group and even lower with higher pregabalin dose (16/31, 5/31 and 3/31 respectively) 3 months after surgical procedure. Therefore concluded preoperative oral pregabalin 75 or 150mg diminishes postoperative morphine consumption and mitigate pain after cardiac intervenetion[18].

More multicenter randomized double-blinded controlled trials with a larger sample size are to be carried out on the subject to explore more about the analgesic potential of pregabalin. It can also be employed in other surgical procedures apart from elective ophthalmological procedures to unfold results, as we have a limitation of ophthalmological procedures only. There is an unnecessary burden on our healthcare system due to prolonged hospital admission and postoperative stay. To encourage daycare surgeries and enhance early recovery protocols alternative analgesics than opioids are to be discovered.

CONCLUSION

Pregabalin has analgesic potential moreover decreased postoperative consumption of opioids and associated adverse effects such as nausea and vomiting. Hence making it a suitable agent for pain relief in ambulatory surgeries.

Conflict of Interest: None.

Authors' Contribution

SA: Conception, manuscript draft. SN: Supervision of data. AA: Manuscript writing. BA: Statistical analysis, RI: Manuscript drafting.

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