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Efficacy of Pregabalin on Postoperative Analsesia after Surgical Removal of Mandibular Third Molar: A Clinical Trial.

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ABSTRACT

KEYWORD: pregabalin, pharmacology, mandible third molar,pain evaluation,first rescue medicine.

I. INTRODUCTION

A mandibular third molar surgical extraction is one of the most routine interventions in Oral and Maxillofacial Surgery due to the highly frequent impaction of these teeth and the multiple associated diseases, mandating their extraction[1]. Surgical removal is usually followed by a wide range of uncomfortable symptoms associated with various postoperative sequelae, including an inflammatory reaction characterized by pain, swelling, trismus, and functional discomfort of the oral cavity, which tend to appear during the first 24–48 h after surgery[2]

The relief of pain has been described as a universal human right but is not always easily achieved[3]. Opioid analgesics are effective but their use is limited because they may have troublesome and serious side effects, and their potential for abuse may lead to regulatory and logistical difficulties[4]. Analgesic drugs are frequently assessed in the dental impaction pain model. This has become one of the primary models used to develop analgesic drugs because it provides a readily available healthy population and a relatively uniform surgical procedure confined to one area of the body[5]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used drugs for postoperative pain after the extraction of impacted third molars because they have fewer regulatory restrictions; however, they are also associated with some adverse effects, which are more likely at higher doses or with longer courses[6].

Pregabalin [S(+)-3-(aminomethyl)-5-methylhexanoic acid] is a newly developed analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). However, pregabalin is not active at several GABA receptors and it does not appear to mimic GABA physiologically[1]. Analgesic drugs are frequently assessed in pain following surgery to evaluate their analgesic properties.

It is believed to bind to the A2- δ subunit of N-type voltage-gated calcium channels, which reduces the release of glutamate thus inhibiting neuronal excitability following tissue injury. It is 3 to 10 times more potent than gabapentin[7]. Its absorption shows a linear pharmacokinetic profile with bioavailability exceeding 90%. Its peak plasma concentration is reached within 1 hour after ingestion, and a steady-state is achieved within 24 hours. Pregabalin is not metabolized and is excreted by the kidneys unchanged[8].

Pregabalin's side effect profile includes tiredness, dizziness, headache, dry mouth, nausea, vomiting, and constipation. Serious side effects may be blurred vision, hives, rash, and itching[9]. Pregabalin was approved as adjuvant therapy for neuropathic pain, partial seizures, and generalized anxiety disorder. Its use has been reported to reduce postoperative pain, analgesic consumption, and analgesicrelated complications following major orthopedic, ENT, and orthognathic surgical procedures[10].

The first animal study, published in 2000, provided evidence of the antinociceptive effect of pregabalin on behavioral responses to visceral pain induced by lipopolysaccharide (LPS) administration[7]. Pregabalin has been used over the past few years as a coadjuvant in the multimodal treatment of post-operative pain. Numerous studies on the effectiveness of post-surgical oral pregabalin have yielded highly contradictory results, and no consensus has been established on the optimal dose regimen[11].

Recent studies have demonstrated the efficacy of pregabalin in controlling postoperative pain after the removal of impacted mandibular third molars. This study hypothesized that postoperative

administration of 75mg oral pregabalin followed by 12 hourly for 3 days produces an effective analgesia compared to tablet placebo.

AIMS: The aim of this study was to assess the analgesic efficacy of oral pregabalin 75 mg on postoperative pain following surgical removal of the impacted mandibular third molar. OBJECTIVES: The objectives of this study were a) To evaluate the intensity of pain using the VAS scale. b) A reduction in total consumption of analgesic medication.

PHARMACOLOGY OF PREGABALIN

Pregabalin (3-isobutyl γ-aminobutyric acid [GABA]) is an analog of the major inhibitory neurotransmitter GABA. Pregabalin does not bind to GABAα or GABAβ receptors and is not converted metabolically to GABA or to a GABA agonist. Like gabapentin, pregabalin's pharmacologic properties are the result of presynaptic binding to the alpha-2-delta subunit of voltage-sensitive calcium channels[7,9].

The active drug substance is У-aminobutyric acid. It is a yellow crystalline solid with a pKa of 4.8. It is highly ionized at physiological pH and has relatively low lipophilicity thereby preventing distribution to fatty tissues[7]. Empirical Formula: C8H17NO2 Molecular weight: 159.23g/mol.

Mechanism of ActionThe precise mode of action of pregabalin has not been fully elucidated, but it does interact with the same binding site and has a similar pharmacologic profile, like gabapentin (1-[aminomethyl] cyclohexane acetic acid). Its main site of action appears to be on the 2-subunit of presynaptic, voltage-dependent calcium channels that are widely distributed throughout the peripheral and central nervous systems[8].The binding affinity for the end potency is six times more than that of gabapentin. Up-regulation of the subunit may play an important role in hypersensitization processes. Pregabalin appears to produce an inhibitory modulation of neuronal excitability, particularly in areas of the central nervous system dense in synaptic connections such as the neocortex, amygdala, and hippocampus[9]. Voltage-dependent calcium channels have been divided into six classes, based on their voltage dependence, kinetics, and sensitivity to a range of drugs. The molecular structure of these functionally identified P-, Q-, N-, L-, R-, and T-type calcium channels have now been determined. N-type calcium channels are thought to have a role in pain sensitization processes[32]. Pregabalin binds potently to the 2-unit and modulates calcium influx at nerve terminals, and, thereby, reduces the release of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine, and substance P[9].

Pregabalin selectively binds to the α2δ-1 and α2δ-2 subunits and despite its original design as a GABA mimetic, pregabalin does not affect GABAα or GABAβ receptor activity. Interestingly, α2δ-1 expression appears to co-localize mainly with excitatory neurons whereas α2δ-2 is found largely in inhibitory neurons[7].

PHARMACOKINETICS: -

ABSORPTION: Pregabalin is rapidly and extensively absorbed after oral dosing in the fasted state, with maximal plasma concentrations occurring ~1 h after single or multiple doses, and steady-state being achieved within 24–48 h after repeated administration.8 The oral bioavailability of pregabalin is high at ≥90% and is independent of dose. The mean elimination t1/2 of pregabalin is 6.3 h and is also independent of dose and repeated drug administration. These findings of consistent dose-proportional pharmacokinetics for pregabalin justify confidence in the prediction of dose-response relationships in clinical practice. 10

DISTRIBUTION: Although pregabalin is not very lipophilic, it can cross the blood-brain barrier (BBB). System L transporters facilitate the transport of large amino acids across the BBB and it has been confirmed that pregabalin is a substrate. This information suggests that system L transporters are responsible for pregabalin uptake into the BBB.8 After oral administration of pregabalin, the reported apparent volume of distribution is roughly 0.5 L/kg.

METABOLISM: Pregabalin does not undergo hepatic metabolism and is not bound to plasma proteins. It is renal excreted, and 98% of the absorbed dose is excreted unchanged in the urine. Pregabalin elimination is nearly proportional to creatinine clearance. Pregabalin clearance is reduced in subjects with impaired renal function. A 50% reduction in pregabalin daily dose is recommended for patients with creatinine clearance (CLcr) between 30 and 60 mL/min compared with those with CLcr 60 mL/min. 9 EXCRETION: Pregabalin is eliminated primarily by renal excretion, the dose should be adjusted for patients with reduced renal function.

DOSAGE AND ADMINISTRATION: - Pregabalin can be administered 2 or 3 times daily. It can be started at 150 mg/day and, although this dose was effective, the recommended effective dose is 300–600 mg/day. The dose of pregabalin should be adjusted downward in patients with renal insufficiency.11.

TOLERABILITY: - Pregabalin is well tolerated and associated with dose-dependent adverse effects that are mild-to-moderate and are usually transient. dizziness and somnolence are the most frequently reported adverse events, with dizziness experienced by 29% of pregabalin-treated patients compared with 9% with placebo and somnolence, experienced by 22% of pregabalintreated patients Dose-dependent weight gain has been reported.8 THERAPEUTIC POTENTIAL: - Acute postoperative pain • Acute spinal surgery • Acute sinusitis surgery Chronic pain • Postherpetic neuralgia • Diabetic peripheral neuropathy • Fibromyalgia Epilepsy Generalized anxiety disorder.

CONTRAINDICATIONS: - Contraindicated in patients with known hypersensitivity to pregabalin.

ADVERSE DRUG REACTIONS: - Most adverse events caused by pregabalin were mild to moderate in intensity. Somnolence and dizziness occurred most frequently (up to 50% and 42% of pts., respectively). The third most common adverse effect was peripheral edema in neuropathic pain trials (19%), ataxia in epilepsy trials (27%), and headache in the anxiety trials (29%). Other adverse effects that occurred in >10% of patients, in decreasing order, were abnormal thinking, asthenia, infection, mouth dryness, accidental injury, diplopia, nervousness, amblyopia, amnesia, diarrhea, and incoordination.8.

DRUG INTERACTION: - The pharmacokinetic profile of pregabalin indicates that it should have a very low potential for drug-drug interactions. Since pregabalin is neither metabolized nor bound to plasma protein, there is no rationale for drug-drug interactions to occur via these mechanisms. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone and may potentiate the effects of ethanol and lorazepam. Co-administration of pregabalin with GBP has been shown to reduce the Cmax for pregabalin (by 18% after multiple-dose administration), but without altering the total exposure to the drug. Gabapentin pharmacokinetics are unaffected by co-administration of pregabalin. 33 The lack of drug interactions means that pregabalin can be safely coadministered with other drugs, and this makes it particularly useful as adjunctive therapy in refractory patients who are already receiving several different AEDs.

Material and method: A prospective, single blinded, randomized control clinical study was done on 60 patients with their informed consent in the Department of Oral and Maxillofacial Surgery, Ahmedabad Dental College and Hospital, Gandhinagar, Gujarat, India. The ethical clearance for the study was taken from an institutionally approved ethical committee. Study Sample: - The study sample consisted of 60 patients who were undergoing mandibular 3rd molar surgical extraction. The study period is 2019-2021.

Inclusion Criteria: - 1. Healthy individuals fit for surgery. (ASA Class I and Class II) 2. Patient aged over 18 years of either sex. 3. Patients having chief complain in relation to the mandibular third molar region and clinical and radiographic diagnosis of an impacted mandibular third molar and which requires surgical removal of mandibular third molar. 4. patients willing for follow up visits on 7th post-operative day were included.

Exclusion Criteria: - 1. patients having clinically significant medical history and falling in category ASA other than 1 and 2 (eg. Systemic infective disease, haematological disease, deficiency of coagulation, diabetes and neoplastic disease) 2. Patient having a history of drug or alcohol addiction. 3. Patient having hypersensitivity to paracetamol, pregabalin, acetylsalicylic acid or any other NSAID and lactose intolerance (Placebo).4. Patient on antidepressant, muscle relaxant, narcotic, antipsychotic, medicine for nausea and vomiting. 5. Acute inflammation or infection associated with impacted third molar. 6. Pregnant and lactating women. 7. Patient who are allergic to amide type of local anesthesia.

Randomizing the samples: - This was a single-blind study. All surgical procedure and post-operative managements were performed by the same surgeon. Signed written informed consent was obtained from all the patients prior to the surgery. Subjects were divided randomly in to two equal groups by random allocationGroup A (Control) (n-30) patients receiving tablet placebo orally 60 minutes postoperatively, every 12 hours for 3 days. Group B (Study) (n-30) patients receiving pregabalin 75mg tablet orally 60 minutes postoperatively, every 12 hours for 3 days.

Pre-operatively routine blood investigation (Hb, BT, CT, RBS) were done Informed consent was obtained before surgery Sample were divided into two group: Group A and Group B. Surgical Procedure: • All the surgical procedures were carried out in the department of oral and maxillofacial surgery by the same surgeon. • Extra oral painting was done by 5% povidone iodine and draped in sterile drape. Intra oral irrigation was done with povidone iodine followed by normal saline. • Inferior alveolar nerve and long buccal nerve anaesthesia was administered using a solution of 2% lignocaine hydrochloride and adrenaline 1:80,000. • Terene Ward's incision was

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used and a triangular full thickness flap with releasing incision on the mesio-buccal aspect of the second molar was routinely designed. • A full thickness mucoperiosteal flap was reflected and the underlying bone was exposed. Then osteotomy and tooth sectioning were done as required. A point of elevation was identified, tooth was luxated by an elevator and then removed. • Debridement of the socket was done with curette and the sharp bone edges were smoothened by bone file. The socket was irrigated with normal saline to remove remaining debris. • Once hemostasis was achieved, the wound was closed by 3-0 nonabsorbable silk sutures. • All patients were given postsurgical assigned drug 60 minutes after surgery.

Pre-operative Evaluations: - Clinical case history record and clinical photographs. - IOPA and Orthopantomograph (OPG) - Examination and assessment of the impacted mandibular third molar tooth. - Routine blood investigation reports (Hb, BT, CT, RBS)

Post- operative Assessment: The patients were evaluated postoperative on 2nd ,4th ,8th ,12th hr on 1st day, 3 rd and 7 th day. 1. Pain: Pain was recorded objectively using VAS (visual analogue scale). Each patient was explained how to measure pain intensity on VAS scale of 0-10, with 0 representing no pain, 1-2 representing mild pain, 3-6 representing moderate pain and 7-10 representing severe pain. Pain was assessed by each patient at 2 nd ,4th ,6th ,8th ,12th and 24 hours on 1st day, 3 rd and 7th day after the completion of surgery. Visual Analogue Scale (VAS) ➢ Time when First rescue analgesic was taken were noted. ➢ Analgesic medications required during 1 st ,2 nd and 3 rd postoperative days and total analgesic required up to 7th postoperative day were noted. Post-operative Management: Materials and Method [Date] 32 ➢ After the surgical removal of lower third molar, all the patients were given standard postoperative instructions. ➢ Patients were followed up 7th postoperative day. ➢ Tablet cefadroxil 500mg every 12 hour for 5 days. ➢ Tablet pregabalin 75 mg every 12 hour for 3 days. ➢ The following rescue medication was prescribed. - Tablet PCM (500mg) ➢ Patients were asked to take analgesics as per requirements but not exceeding the maximum dosage and asked to note down the time of taking rescue medication and to inform the doctor. ➢ Patients were also asked to note adverse events occurring during the first 48 hours of observation period. ➢ 0.12% chlorhexidine mouth rinses twice a day, 24 hours after surgery for 15 days was advised to the patient. ➢ On the 7th postoperative day suture removal was done.

II. OBSERVATION AND RESULTS:

This study included 60 patients who underwent surgical removal of the lower third molar in our department. Subjects were divided into two groups by random allocation using the Lottery method. Group A (Control Group) - Patients receiving placebo tablet orally 60 minutes postoperatively subsequently 12 hr per day for 3 days. Group B (Study Group) - Patients receiving 75mg pregabalin tablet orally 60 minutes postoperatively subsequently 12 hr per day for 3 days. The pain was assessed in patients, following the surgical removal of impacted lower third molars under local anaesthesia. The pain was assessed on the 2 nd ,4 th,6th,8th,12th, and 24th hours,3rd and 7th day postoperative days. All the observations were noted and tabulated in a master chart. Mann Whitney U, Chi-square test and Friedman test was used for statistical analysis the value of 0.05 was considered statistically significant for all analyses. $P < 0.05$ = Significant $P > 0.05$ = Not significant 1.

Demographic analysis: A. The sex distribution. There were 26 male and 34 female patients. In the Control Group, there were 12 males 18 females. In the Study Group, there was 14 male 16 female. (Table- 1) (Graph- 1). the p (>0.05) value was insignificant which infer there was equal distribution in both groups. B.

Mean age of patients. The mean age of patients in the Control group was 31.13 ± 8.58. And mean age of patients in the Study group is 34.07 ± 8.97. p value >0.05. (Table-2) (Graph- 2). there was statistical insignificance which infers that it does not have any effect on the outcome of the study.

Class and position of impacted mandibular third molars: There were 15 impacted mandibular third molar in class 1 position A:10 in Control Group and 5 in Study Group (p = >0.05value:), 14 in Class 1 position B in Control Group were 7and 7 in Study Group. 7 in Class 2 position A: 4 in Control Group and 3 in Study Group. 22 in Class 2 position B: 8 in Control Group and 14 in Study Group, class 2 position C were 1 in each group. (p = >0.05). There were 26 Mesioangular impacted molars: 13 in Group A and 13 in Group B. 14 Distoangular impacted molar: 5 in Group A and 9 in Group B. 11 horizontal impacted molars: 8 in Group A and 3 in Group B. 9 vertical impacted molar: 4 in Group A and 5 in Group B. (Table 2).

3. Comparison of duration of surgery: The mean duration of surgery was 49.56 minutes for the A group and 46.83 minutes for the B group for the duration of surgery. p value >0.05. (Table 4) (graph

3) There was no significant difference in the demographic factor, mean duration of the surgery and difficulty index of surgery among the group.

4. Pain Assessment (Visual analogue scale): Subjective assessment by Mann-Whitney U test amongst 2 groups showed significant p value from 2nd hour to 7 th day. Amongst the Control group and Study group, the P value was @@@@ The intragroup comparison was conducted in Control groups using the Friedman test. Subjective assessment of pain during 2 nd hr (mean 4.47 ± 0.86), 4th hr (mean 4.33 ± 0.76), 8 th hr (mean 3.93 ± 0.83), 12th (mean 2.60 ± 1.07), 1 st day (mean 2.07 ± 1.11), 2nd day (mean 1.40 ± 1.19), 3rd (mean 0.80 ± 0.99) and 7th day (mean 0) showed that there was statistically significant difference Control group (table-5) (Graph-4(c). The intragroup comparison was conducted in the Study Group using the Friedman test. Subjective assessment of pain during 2 nd hr (mean 2.93± 1.34), 4th hr (mean 2.67 ± 0.92), 8th hr (mean 2.23 ± 1.07), 12th (mean 1.40 ± 1.38), 1st day (mean 1.13 ± 1.19), 2nd day (mean 0.70 ± 0.99), 3rd day (mean 0.43 ± 0.73) and 7 th day (mean 0.33 ± 0.61) showed that there was a statistically significant difference in Study group. (Table-6) (Graph-4(d)).

5. Comparison of time to first rescue analgesic amongst groups and total consumption of rescue analgesic The mean time to first rescue analgesic medication was 2.23 hours for the Control group and 5.67 hours for the Study group, there was a statistically significant difference between the Control group and the Study group for the time to take the first rescue analgesic. p value is

The mean total consumption of rescue analgesic up to 7th postoperative days period was 7.17 for the control group and 1.36 for the Study group, which was statistically significant between the Control group and Study group B (P-<0.005).(Table- 8, Graph-5b)

6. Consumption of rescue analgesic on 1st ,2 nd, and 3 rd day: The rescue medication was taken 1 st, 2nd and 3rd day were compared with Mann-Whitney U test. The mean rescue analgesic taken on the 1 st day is 2.17,the 2 nd day is 2.13 and the 3 rd day is 2.03 for the Control group. The mean rescue analgesic taken on the 1 st day is 0.93, 2 nd day 0.46 and 3 rd day is 0.23 for the Study group. The value of p<0.001.There was a statistically significant difference between the Control group and the Study group for consumption of rescue analgesia drugs. (Table-9) (Graph-6).

7. Adverse effect in amongst the groups: Adverse effects like dizziness, nausea, vomiting, motion sickness, and headache were seen in the study group. Dizziness was seen in 3 patients, nausea and vomiting in 2 patients, headache in 1 patient and motion sickness in 2 patients. There was no adverse effect seen in the control group.

III. DISCUSSION:

The surgical removal of the impacted mandibular third molar is a common procedure that has been routinely performed in oral and maxillofacial surgical practice on an outpatient basis. Moderate to severe pain associated with this surgical extraction is a frequent complaint that may affect the patient's quality of life. A surgical tissue injury induces a complex interaction between local inflammatory and general neurohumoral responses. The pain usually peaks 6-8 hours after third molar surgery, is markedly diminished after 12 hours, and gradually disappears within a few days. Surgical procedure is associated with acute tissue damage resulting in the production of prostaglandins. Prostaglandins are synthesized rapidly following tissue injury and appear in significant concentrations just one hour after trauma. 38 These activated allogenic substances stimulate polymodal nociceptors on C fibers. Substance P stimulates nitric oxide (NO) synthesis in vascular endothelium. Nitric oxide produces vasodilation and leakage of the vessel wall. Mast cells release platelet-activating factor, which in turn releases serotonin (5- hydroxytryptamine) from platelets. Serotonin activates the nociceptor and causes pain. If nociceptive inputs persist, there is modulation of CNS through activation-dependent plasticity leading to peripheral sensitization. This peripheral sensitization causes a reduction in pain threshold at the site of injury known as primary hyperalgesia. Due to lowered pain threshold and increased peripheral neuronal excitability, nor nociceptive stimuli can trigger modulation of central pain pathways. Protracted peripheral noxious stimulation causes wind up and activation of NMDA (N-methyl-D-aspartate) receptors on central multireceptive WDR neurons central nociceptive WDR neurons are activated which have thus significant effects on CNS via paleo thalamic tract up to thalamus and cortex leading to sensitization of dorsal horn neurons and trigeminal nucleus neuron. This mechanism is known as central sensitization, there is an increased sensitivity to mechanical stimuli, in a region surrounding the area of injury. which is known as secondary hyperalgesia. Both primary and secondary hyperalgesia is involved in postoperative pain.

Regarding the reduction of postoperative pain sensations, many pharmacological strategies have been developed to reduce peripheral and

central sensitization. The Spanish Association of Major Outpatient Surgery has suggested four major groups of drugs, that can be used against acute postoperative pain: antipyretic and anti-inflammatory analgesics (paracetamol, metamizole, NSAIDs), opioid analgesics (tramadol, codeine), local anesthetics, and analgesic coadjuvants. Coadjuvants are a heterogeneous group of drugs used to enhance the action of conventional analgesics including, gabapentinoids (gabapentin, pregabalin), α-2 agonists (clonidine), NMDA receptor antagonists (ketamine, dextromethorphan), and glucocorticoids (dexamethasone). [11]

The possible mode of action of pregabalin appears to be on the α2-δ subunit of presynaptic, voltage-dependent calcium channels that are widely distributed throughout the peripheral and central nervous systems. The binding affinity for the α2-δ subunit, and potency, is six times more than that of gabapentin. Up-regulation of the α2-δ subunit may play an important role in hypersensitization processes. Pregabalin appears to produce an inhibitory modulation of neuronal excitability, particularly in areas of the central nervous system dense in synaptic connections such as the neocortex, amygdala, and hippocampus. Pregabalin binds potently to the α2-δ subunit and modulates calcium influx at nerve terminals, and, thereby, reduces the release of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine, and substance P. Serotonin and substance P are released due to acute postoperative pain, which is reduced by pregabalin.[8]

Pregabalin is currently used against peripheral neuropathic pain and in the treatment of partial epileptic seizures, post-herpetic neuralgia, diabetic peripheral neuropathy, fibromyalgia and generalized anxiety disorder. 10 It has been introduced as an adjuvant in the multimodal management of postoperative analgesia following reports of its effectiveness for acute postoperative pain in minor gynecological surgery, laparoscopic cholecystectomy, and tonsillectomy. 19 The finding of clinical trials of pregabalin in acute postoperative pain has been inconsistent. So, we decided to study the efficacy of pregabalin in postoperative pain after surgical removal of impacted mandibular molar. A single-blinded study was conducted in our department of oral and maxillofacial surgery, on Sixty patients to assess the effectiveness of pregabalin on postoperative pain after surgical removal of mandibular third molar surgery. The patients were divided into two groups, the Control Group which received a placebo 60 min postoperatively, subsequently, 12 hourly for 3 days and the Study Group received tab pregabalin 75 mg orally 60 min postoperatively subsequently every 12 hourly for 3 days.

A lower pregabalin dose of 75 mg was chosen in this study. To reduce the likelihood of side effects, especially during postoperative days of surgery. which was supported by Hill and colleagues.1 They found that patients taking pregabalin 300 mg after dental surgery had a longer duration of analgesia but more frequent adverse events and complications. Even pregabalin 100 mg can cause significant side effects such as dizziness and somnolence in an ambulatory population.

In the given study, drugs were given postoperatively. This was supported by cheung et al. 17 who additionally reported a greater analgesic efficacy with postoperative versus preoperative administration of this dose. However, Kim et al.34 administered 75 mg pregabalin 1 h before surgery and 12 h afterward and found that a perioperative dose of pregabalin was effective to reduce postoperative pain in patients undergoing mastectomy. The patients were evaluated postoperatively on 2nd,4th,8th,12th, 24th -hour, 2 nd, 3rd and 7th day using the Visual Analogue Scale. Amongst the Control group and the Study group, the P-value was <0.001 at 2nd, 4th,8th, and 12th postoperative hours. P value was <0.05.We observed that mean pain intensity was well controlled in the study group than in the control group at all intervals of time. Same as our study, Pakravan et al. 35 reported that VAS scores were highly similar in the 75-mg pregabalin and 300-mg gabapentin groups and always lower than those in the placebo group. Park et al.36 reported that VAS pain scores were lower in the 300-mg pregabalin group than that in the 4-mg diazepam group on days 1–4 post-surgery, which were similar between the groups on days 5 and 6 and were again lower in the pregabalin group on day 7.

In our study, the total rescue analgesic was significantly reduced during 1 st, 2nd and 3rd postoperative days in the Study groups compared with the control group. This predicts not only less pain level during the initial postoperative period, but also lowered the intensity of pain during the days after surgery. Numerous studies have evaluated the consumption of rescue analgesics as a measure of postoperative pain control, which was supported by Ahiskaliolgu et al, who reported a significant reduction in fentanyl consumption at 24 h in the 150-mg pregabalin versus placebo groups ($p = 0.004$), and Cillo et al, who described a significant ($p < 0.05$) reduction in i.v. morphine during the immediate post-operative period in the 150-mg pregabalin group, daily morphine consumption also remained lower during the next 7

days. Sagit et al. reported a significantly higher total consumption of rescue analgesics by the placebo group than that by the 75 or 150-mg pregabalin groups ($p < 0.001$), with no difference between the pregabalin groups

However, Cheung et al.17 found no significant differences in the consumption of rescue analgesics between the administration of 75-mg pregabalin 1 h before or immediately after the surgery. Olmedo-Gaya et al.18 the same number of patients required rescue medication in the control and 75-mg pregabalin groups, but fewer pills were consumed by the latter ($p = 0.021$).

In our study, adverse effects like nausea, motion sickness, headache, diarrhoea, and vomiting were seen in the study group. No adverse effects were seen in the control group. Most adverse events caused by pregabalin were mild in intensity. Which was supported by shneeker et al.[10] They were dosedependent and occurred within the first 2 weeks of treatment. The most common adverse events were related to the central nervous system, and these were responsible for most discontinuations. Somnolence and dizziness occurred most frequently (up to 50% and 42% of pts., respectively) Olmedo-Gaya et al.18 reported that adverse effects (somnolence and dizziness) were more frequent and intense in the 75-mg pregabalin group than those in the placebo group ($p < 0.001$).

However, Meek et al[.37] observed no differences in adverse effects reported by patients between the 75-mg pregabalin and placebo groups, and none were severe. Hill et al.[1] found that the intensity of adverse effects was similar among the placebo, ibuprofen, and 50-mg pregabalin groups but higher in the 300-mg pregabalin group. Hence, based on the present study and as per the support of the literature, it can be stated that 75 mg pregabalin tablet given postoperatively provides significant analgesic effectiveness, longer free intervals in terms of time required to first rescue analgesic compared to the placebo group. However, further research is required on the efficacy of pregabalin in the control of postoperative dental pain and on associated adverse effects.

IV. SUMMARY AND CONCULSION:

A prospective, single-blind, case-controlled clinical study was carried out in 60 patients who were to undergo surgical removal of impacted mandibular third molars. All cases were done in the Department of Oral and Maxillofacial Surgery, Ahmedabad Dental College & Hospital. Among the selected patients, patients were divided into the following group: In the control group, patients were given a placebo orally postoperatively. Study group patients were given tab pregabalin 75 mg 60 min postoperatively followed by 12 hourly for 3 days. Following surgery, the pain intensity was assessed with VAS postoperatively on the 1 st, 2nd,4th, 8th, 12th 24th hour 2nd, 3rd and 7 th day. All patients were prescribed rescue analgesics and were advised to take analgesics as per requirements but not exceeding the maximum dosage per day. Following surgery pain was assessed. Based on all the observation and statistical analysis, we concluded that: Analgesic efficacy of 75 mg pregabalin was found to be superior when given postoperatively as compared to placebo in terms of pain intensity at the time of first rescue analgesic medication was taken and total rescue analgesic consumption. However, the limitation of the study is the small sample size, single-blind study and selection of unilateral cases, Further studies with a larger sample size, different administration time, modifications like keeping the study double-blind and doing a split-mouth study can be done to get more conclusive evidence regarding the effect of the study drug.

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