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ORIGINAL ARTICLE

# Comparison of naproxen and combination therapy (naproxen and gabapentin) in post extraction pain relief.

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**ABSTRACT… Objective:** To evaluate the efficacy of using combination drug treatment to relieve post extraction pain of impacted mandibular third molar by using Naproxen plus Gabapentin versus Naproxen alone. **Study Design:** Randomized Control study. **Setting:** Dental Clinic OPD of Bhitai Dental and Medical College, Sindh, Pakistan. **Period:** 1st December 2018 to 30th May 2019. **Material & Methods:** The procedure for extraction was carried out under Local Anaesthesia (2% lignocaine hydrochloride with 1:100,000 adrenaline) at dental clinic OPD of Bhitai Dental and Medical College. Some extractions were performed in Closed Extraction technique while in some patients standard surgical procedure was used which consist of triangular muco – periosteal flap on buccal surface and lingual retraction of soft tissue followed by bone removal. For Pre – Operative and 24-Hour Post – Operative Pain status assessment Visual Analogue Scale and Wong Baker's Face Pain Rating Scale. **Results:** Combination therapy (Naproxen and Gabapentin) was effective in significant pain reduction at 12 Hour and 24-Hour Post Extraction period. With 26 patients out 31 presented with Pain Scale of 0 on combination therapy while only 3 out of 31 for naproxen alone after 24 hours. All patients received a single dose of study medicines from the hospital pharmacy. In demographic data, there were 47% (n=29) males and 53% (n=33) females with mean age group of 27.89. Comparing the pain response between the genders, males presented slightly faster pain relief with time as to the females. **Conclusion:** Enhanced effect of combination therapy of naproxen with gabapentin in reducing post extraction pain of impacted mandibular third molar with respect to naproxen alone.

**Key words:** Combination Therapy, Gabapentin, Naproxen, Post Extraction Pain.

## INTRODUCTION

Wisdom tooth extractions are one of the most common surgical procedures performed in dental surgery. Impaction of the third molars in divergent directions is commonly observed in the patients due to lack of space or presence of a barrier; hence, failing to maintain normal functional position. Current modernized technology helps to visualize the position of the impaction in a 3D imaging CT scan to avoid the nerve impingement and damaging the neighboring structure during the manipulation of the surrounding soft tissue and bone.[1] Impaction usually occurs at ages between 18 and 24 years imposing a risk of infection, deep caries, periodontal disease, cysts, or tumors.[2] Acute postoperative pain and inflammation are commonly associated with the impacted third molars; hence, initial investigation before the surgical procedure is necessary for better post-operative measures. Pain, trismus, swelling with or without pus are the most common complaints by patients after the impacted mandibular third molar surgical extraction.[2] Acute Pain with the manifestation of inflammation after extraction of impacted mandibular third molar results from tissue damage either accidentally or because of surgery. The pain usually lasts for moderate and short duration except in traumatic extractions. Several methods are employed in the management of these issues of patients such as surgical closure with or without drains, use of analgesics, corticosteroids, and antibiotics.[3] The most prescribed drugs in post-extraction are paracetamol, NSAIDs alone or in combination with drugs having analgesics and/or anti-inflammatory properties to reduce post-extraction complaints.

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The NSAIDs have a dual action comprising of analgesics and anti-inflammatory properties. Several studies have been conducted with variating regimens to control/ relieve the post-operative pain and complications.[4] The outcomes obtained defined no significant differences in pain relief of post extraction pain by administering analgesics before or after the procedures; however, other studies found that NSAID such as diclofenac potassium in combination with corticosteroid displayed superior efficacy in modulating the pain than diclofenac alone.[5] Naproxen is another commonly prescribed NSAIDs by the clinicians. Naproxen is a derivative of propionic acid associated with the aryl acetic acid group with analgesic and antipyretic properties. The generic names for naproxen and naproxen sodium are (S)-6-methoxy-α11 methyl-2-naphthaleneacetic acid and (S)-6-methoxy-α-methyl-212 naphthaleneacetic acid, sodium salt, respectively. The sodium salt chemical attachment to the naproxen allows the rapid absorption of the drugs for immediate analgesic effect. The naproxen anion mechanism of action is associated with prostaglandin synthetase inhibition.[6]

NSAIDs in chronic user produces many gastrointestinal, renal, and hepatic problems. Nevertheless, various methods have been employed to decrease these side effects such as minimum dose, short-duration therapy, combination with other pain modulators such as antiepileptic agents (gabapentin). Gabapentin is an antiepileptic drug often used in the management of neuropathic pain. Gabapentin, the chemical formula is 3-alkylated analogue of gamma-amino butyric acid (GABA), which action mechanism is modulated based on alpha-2-delta calcium channel subunits. Many studies have supported the evidence of Gabapentin in reducing post-operative pain.[7]

Studies show that gabapentin plus naproxen act synergistically and provide an additive effect in reverting hyperalgesia associated with peripheral inflammation.[8] The use of gabapentin in combination with naproxen provides therapeutic benefit especially in the elderly population with the risk of adverse renal and/or gastrointestinal effects of NSAIDs for treatment of inflammatory pain. The principal benefit of the combination of gabapentin and naproxen depends upon the ability to administer a very low dose of each medication in combine form to achieve a significant decrease in pain. The available research reports unveil that, naproxen in combination with omeprazole acts promising pain relieving agent during third molar extraction. However, in spinal surgeries naproxen alone seems least effective. Current research is designed to evaluate post extraction pain relief effect of the naproxen in comparison to Gabapentin. The purpose of this study was to evaluate the efficacy of using combination drug treatment to relieve post extraction pain of impacted mandibular third molar by using Naproxen plus Gabapentin versus Naproxen alone.

## MATERIAL & METHODS

Current six-month (December 2018 -May 2019) duration based experimental research study was conducted at Dental Clinic OPD of Bhitai Dental and Medical College, Sindh, Pakistan. Patients in inclusion criteria fitting an ASA classification of P1 or P2 of both gender male and female with an age range between 20 – 35 years. Whereas patients showing hypersensitivity to any drugs, Patients in ASA Classification of P3, P4, P5 and P6, Pre – operative habitual users of analgesics or psychiatric drugs or other drugs are known to modulate pain, alcohol or other substance abusers were excluded from the study. Patients were randomized into two treatment groups by even & odd outpatient department (OPD) ticket number. Tab Amoxicillin: 500mg, Clavulanic Acid: 125mg (Augmentin, GlaxoSmithKline) two times a day for 3 days was prescribed to both groups along with their analgesics. i). Naproxen alone 1000 mg/day in 12 hourly divided doses (Odd OPD Number). ii). Combination of gabapentin 300 mg/day in 8 hourly 3 doses of 100 mg and naproxen 500mg/day 24 hourly (Even OPD Number). This very small dose of gabapentin was used in study based on the finding from study[9] which showed Gabapentin 250 mg was superior to placebo in treatment of acute post-operative pain, however gabapentin 250 mg is not clinically

useful as alone in acute post – operative pain and there is no evidence that any analgesic effect of gabapentin is dose dependent. That's why it was studied to find any difference in management of post – operative pain of extraction of impacted mandibular third molar.

About 62 Patients met the inclusion criteria for the impacted third molar surgical procedure regardless of their classification of impaction at Dental Clinic OPD of Bhitai Dental and Medical College, Sindh, Pakistan. The post operatively designated prescription was administered to patients who underwent elective oral surgery for removal of mandibular third molars which were fully or partly impacted in bone. The procedure for extraction was carried out under Local Anaesthesia (2% lignocaine hydrochloride with 1:100,000 adrenaline) at dental clinic OPD of Bhitai Dental and Medical College. Some extractions were performed in the Closed Extraction technique while in some patient's standard surgical procedure was used which consist of triangular muco – periosteal flap on buccal surface and lingual retraction of soft tissue followed by bone removal with bur, sectioning if needed, elevation of roots, debridement, followed by normal saline irrigation, suturing with 3/0 Silk sutures.

Informed consent obtained from all included patients was followed by familiarizing them with 10 – point Visual Analogue Scale (VAS) pain score and 5 Point Wong – Baker "Faces" Pain Rating Scale. VAS ranged from 0 = no pain to 10 = unbearable pain. Faces pain rating scale was ranged from 0 = No Hurt to 5 = Hurts Worst. Pre-operative pain severity was assessed and recorded. Charts with Visual Analogue Scale were provided to the patient to record their pain at 4, 6, 12 and 24 hours by themselves at their home. Patients were demonstrated until fully understood by them the method of recording.

The statistical analysis of the obtained data was performed using SPSS 16.0. The mean and standard deviation was analyzed to compare the efficacy of both regimens administered. The VAS scale data were analyzed using the chi-square to reject the null hypothesis.

## RESULTS

A total of 62 patients were recruited at the dental clinic OPD of Bhitai Dental and Medical College for extraction of impacted lower 3rd molar under local anesthesia. Those patients who fulfilled the inclusion criteria were randomly distributed into two equal groups (n= 31) each given a specific regimen; group A combination therapy (naproxen and gabapentin) and group B naproxen alone. Patients were directed to take their prescription 30 minutes after extraction to counteract the effect of pain after dissociation of the local anesthesia effect. Post-operative follow-up for pain relief was assessed on certain parameters such as the pain intensity difference at 4, 6, 12 and 24 hours after the surgical procedure. The assessment was performed by the principal investigator. All patients received a single dose of study medicines from the hospital pharmacy. In demographic data, there were 47% (n=29) males and 53% (n=33) females with mean age group of 27.89. Comparing the pain response between the genders, males presented slightly faster pain relief with time as to the females. The drug regimen was given to the patient as per the designated group, prescription of drugs based on gender is shown in (Table-I). For equal distribution of the data, the random allocation was performed, 31 patients have been prescribed Naproxen alone and 31 were prescribed with combination therapy consisting of naproxen and gabapentin. Out of 31 patients, taking Naproxen alone, there were 32% of males and 68% of females, while in combination therapy, 61% males and 39% females. The preoperative pain status was evaluated based on the Visual Analogue scale by patients and Facial Pain Rating Scale by Dental Surgeon and results showed Mean preoperative pain on VAS was 5.81 while on Wong-Baker Facial Pain Rating Scale it resulted in a mean of 3.24 as shown in (Table-II & III). Post-operative pain status results showed that overall pain score was decreasing with a mean pain score of 3.55, 2.76, 1.34 and 0.53 at 4, 6, 12 and 24 hours respectively. All patients suffered pain reported that reduced pain intensity after the wearing of anesthesia postoperatively. Initially, at 4 hours period post-extraction, both regimes

do not significantly decrease the pain. However, after 4 Hours, 26 patients who took combination therapy reported the absence of pain on Scale with 0, while only 3 patients with Naproxen alone. 4 patients reported pain on VAS 1 after taking combination therapy, while 15 patients reported on VAS 1 after taking naproxen alone after the 24 hours. 1 patient reported with VAS 3 after taking Naproxen while no patient was observed in VAS 3 or more in combination therapy. Post – Operative mean Pain Scores based on Drug Regime and Time is shown in (Figure-1). From results (Figure-2) it appeared that significant changes in pain modulation with combination therapy occurs at a 12-hour period of taking drugs before that naproxen produced significant pain modulation with respect to combination drugs. The absence of pain (VAS = 0) after 6 hours was more prevalent in patients taking combination therapy. Post-operative severity of pain (VAS = 1 – 2) was similar until a 6-hour period in both regimens; however, after 12 hours there was a decrease in the severity of pain.

After evaluation of mean pain scores in post-operative period, it appears that mean post-operative pain was significantly reduced with combination therapy as shown in The severity of pre-treatment means pain score was not significant in both groups; in Naproxen alone patients were 5.77, while for combination therapy was 5.84. The mean age group in Naproxen alone group was 27.58, while for combination therapy it was 28.19.

| Sex | | Pain 12 Hours | Pain 24 Hours | Pain 6 Hour | Pain 4 Hour | Pre-Operative Pain VAS |
|---|---|---|---|---|---|---|
| Male | Mean | 1.21 | .41 | 2.59 | 3.41 | 3.28 |
| | N | 29 | 29 | 29 | 29 | 29 |
| | Std. Deviation | .675 | .501 | 1.018 | 1.053 | 1.623 |
| Female | Mean | 1.45 | .64 | 2.91 | 3.67 | 3.21 |
| | N | 33 | 33 | 33 | 33 | 33 |
| | Std. Deviation | .711 | .549 | 1.100 | 1.164 | 1.495 |
| Total | Mean | 1.34 | .53 | 2.76 | 3.55 | 3.24 |
| | N | 62 | 62 | 62 | 62 | 62 |
| | Std. Deviation | .700 | .535 | 1.066 | 1.111 | 1.544 |

**Table-I. Comparison between the gender in relation to pain response.**

**Descriptive Statistics**

| | N | Min. | Max. | Mean | Std. Deviation |
|---|---|---|---|---|---|
| Pre-Operative Pain Wong – Baker Facial pain rating scale | 62 | 1 | 5 | 3.24 | 1.544 |
| Valid N (listwise) | 62 | | | | |

**Table-II. Pre-Operative VAS pain status**

**Pre-Op VAS**

| | | |
|---|---|---|
| N | Valid | 62 |
| | Missing | 0 |
| Mean | | 5.81 |
| Std. Deviation | | 3.109 |

| Time | Drug Regime | Mean | Std. Deviation | P-Value |
|---|---|---|---|---|
| 4 Hour | Naproxen | 3.68 | 1.166 | 0.365 |
| | Naproxen and Gabapentin | 3.42 | 1.957 | |
| 6 Hour | Naproxen | 2.84 | 1.186 | 0.556 |
| | Naproxen and Gabapentin | 2.68 | 0.945 | |
| 12 Hour | Naproxen | 1.48 | 0.677 | 0.103 |
| | Naproxen and Gabapentin | 1.19 | 0.703 | |
| 24 Hour | Naproxen | 0.94 | 0.359 | 0.000 |
| | Naproxen and Gabapentin | 0.13 | 0.341 | |

**Table-III. Post-Operative mean pain score on wong baker face pain rating scale with respect to time and regime (Student T-test).**

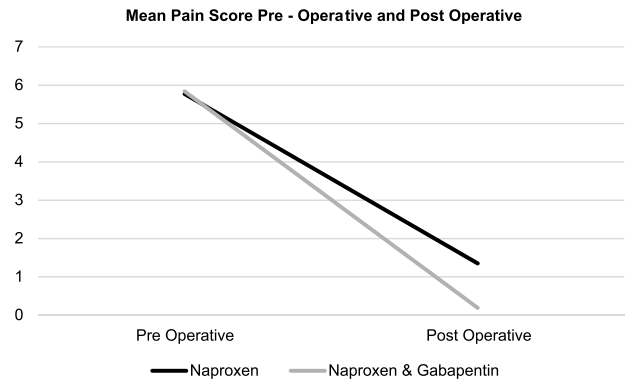


**Figure-1. Mean pain scores before and after drug regime**

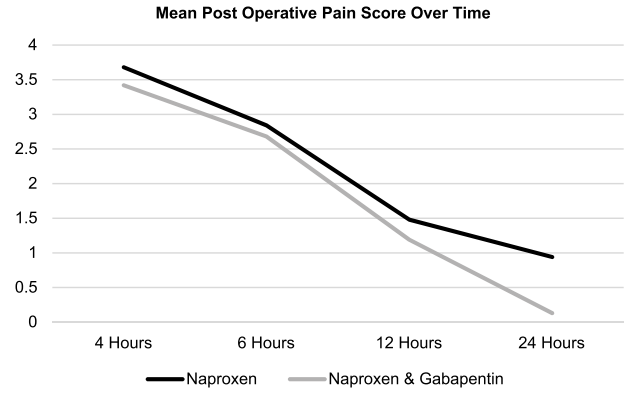


**Figure-2. Mean pain score with respect to time**

## DISCUSSION

The present study intended to demonstrate the effectiveness of combination therapy of Gabapentin and Naproxen over Naproxen alone on pain relief after impacted lower third molar surgery. The analyzed results displayed a significant difference between the two regimens at 24 hours only (p-value $< 0.01$). Initially, both the regimens were acting equally; however, after 12 hours the combination therapy had an immediate effect relative to naproxen alone. Nevertheless, the null hypothesis cannot be rejected completely. A multitude of explanations can be provided for the computed results.

Post third molar extraction has turned into the often-utilized model in the investigation of acute pain clinical trials since third molar surgical extraction is one of the common dental procedures to be performed with an adequate quantity of patients in a short time along with sensitivity.[10] The consistency of the patient sample assisted in producing an unbiased outcome. Measuring analgesic effectiveness is generally done through a comparison of patient's subjective pain assessment before and after administration of the analgesics. Therefore, the wisdom tooth surgical extraction can be readily classified, and the information acquired in the dental pain model supports the sensitivity of the clinical trials and is therefore helpful in predicting the overall analgesic effects of drugs.

The pharmaceutical approach explains that the COX inhibitors act through inhibiting the action of COX while reducing prostaglandin production both in the spinal cord and at the periphery. This reduces the inflammatory reactions and pain at the periphery. Moreover, tissue damaging during the surgical procedure causes the release of inflammatory chemical mediators whilst causing hyperalgesia that is a decrease in pain threshold and an increase in sensitivity to stimuli. Whereas gabapentin acts as an anxiolytic, block the activity of N-methyl-D-aspartate (NMDA), a-amino-3-hydroxy-5- methyl-4-isoxazoleproprionate (AMPA) and metabotropic receptor which causes hyperalgesia and allodynia, respectively.[11]

The peak effect of Gabapentin is reached within 2 hours whereas NSAIDs have an immediate effect with complete analgesic effect in one week.[12]

According to our findings, combination therapy provided a significant reduction in pain severity at 12-hour post-treatment period with mean pain scores of 1.48 for naproxen versus 1.19 for combination therapy at 12-hour post-extraction period on Wong Baker's Face Pain Rating Scale, while after 24 hours it resulted in 0.94 for Naproxen versus 0.13 for combination therapy. However, a slight difference was observed with no significance on VAS pain intensity scale after 24 hours in combination therapy ($n=0$) vs the Naproxen alone ($n=3$).

Several randomized studies demonstrated that the third molar surgery results in moderate to severe pain during the initial 12-hour post-

extraction period; therefore, clinicians employed the drug administration through modifications in the regimen to decrease the pain intensity with minimal side effects of drugs.[13] Few studies assessed the effect of preoperative administration of the NSAIDS and gabapentin drug that displayed an immediate pain relief after wearing off the anesthesia compared to the postoperative administration.[14] Nevertheless, in the present study presented effectiveness with combination therapy of gabapentin with naproxen to provide pain relief with minimum side effects of individual drugs at 24 hours period. Therefore, signifies that initially, the gabapentin did not have an immediate effect; however, its effect was evident after a 12hr period.

Recent studies also provided the benefits of using Naproxen with gabapentin, which results in a synergistic effect in pain modulation. The synergistic effect for gabapentin with naproxen is unlikely to be caused by pharmacokinetic properties because in literature each drug did not alter the levels of each other Furthermore, literature revealed that females present with raised somatization, sensitivity, and intolerance for various types of pain due to higher prostaglandin activity.[15] Thus, increased sensitivity to the COX inhibitors allows the women system to respond immediately to the drugs compared to the men. Similar results were revealed in another study that women reported no pain relief after 2 hours compared to men because of the influence of estrogen or other sex hormones on COX-2; however, further investigation is necessary.[14] In the present study, the mean value of the male reporting pain decreased slightly more swiftly than the females; however, there was no significant difference appreciated between the genders.

Despite the efficacy of the combination therapy, certain limitations of the study should be addressed in future studies. Firstly, a larger study population is required to examine the side effects and drug interactions of this combination. Secondly, the age range selected was limited to evaluate the response to the drug in relation to age. Lastly, the pain is assessment is subject and varies person to person depending upon the pain threshold of individual that needs to be taken into consideration.

Nevertheless, taking naproxen alone effectively reduces pain and inflammation in an adult after surgical procedure with estimated pain scores infrequently raising more than mild pain. Therefore, the clinical recommendation for an immediate effect after anesthesia wearing off is preoperative naproxen drug administration while postoperatively a combination therapy is beneficial.

## LIMITATIONS

Current study was limited to the patients ages 25-35 years visiting Bhitai Dental and Medical College, Sindh, Pakistan. Further, study was limited to small population of the patients. However, study reported outcomes are valid for small group of populations in local settings.

## CONCLUSION

This study resulted in an enhanced effect of combination therapy of naproxen with gabapentin in reducing post extraction pain of impacted mandibular third molar with respect to naproxen alone.

## CONFLICT OF INTEREST

For this study, we did not receive any funding from Pharmaceutical Companies.


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| 3 | Arfat Bashir Soomra | Data analysis suggestions, Data interpretation. | |
| 4 | Fida Baloch | Drafting the manuscript experiments and patient follow-up, data analysis. | |
| 5 | Abdullah Alarifi | Study design, Drafting discussion, Data analysis. | |
| 6 | Ali Maqbool | Study design, Patient selection, data collection, experimental work. | |