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TO EVALUATE THE SAFETY AND EFFICACY OF ETIZOLAM AS ADD ON THERAPY WITH NAPROXEN SODIUM IN AN ACUTE TREATMENT FOR EPISODIC TENSION TYPE OF HEADACHE.

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ABSTRACT

Background: Nonsteroidal anti-inflammatory drugs (NSAIDS) are used for acute treatment of episodic tension type headache(ETTH).Benzodiazepines are also commonly used for the treatment of TTH, however, there were very few randomized controlled trials (RCTs) recommending the use of these drugs. This study was undertaken to evaluate the safety and efficacy of etizolam in combination with a non-steroidal anti-inflammatory drug as an acute treatment of ETTH. **Methods:** We had included 60 patients diagnosed as per criteria of the International Classification of Headache Disorders-II. Patients were randomized into two groups: NSAID alone (naproxen sodium 250 mg) and NSAID plus etizolam (naproxen sodium 250 mg, etizolam 0.5mg) for the management of acute episode of tension type of headache. Improvement in Visual Analogue Scale (VAS) at two hrs of administration of drugs was the primary end point in this study. Changes in four-point verbal functional impairment scale at the base line and at the end of 2hr and reported adverse effects were also recorded. **Results:** Both groups showed

a significant fall in Visual analogue scale for headache, four point verbal functional scales. The group receiving etizolam along with NSAID showed better response rate than NSAID alone .There was no significant difference in adverse effects between the groups. **Conclusion**: Combination of NSAID and Etizolam is useful and safe for the management of acute episode of ETTH.

KEYWORDS: Headache, ETTH, etizolam, NSAIDS.

INTRODUCTION

Tension type headache (TTH) is one of the most widespread of headache disorders and least studied primary headache disorders. The Headache Classification Committee of the International Headache Society (IHS) introduced the term 'tension-type headache'in 1988 and defined the diagnostic criteria for classification. Tension-type headaches have been classified in two clinical forms: episodic, for which the pain is present for less than 15 days per month, chronic for which pain is present for at least 15 days per month (for at least six months).[1] These headaches are characterized by mild to moderate bilateral pain that is described as dull, aching and band like. Its lifetime prevalence in the general population ranges in different studies from 30 to 78%.[2]

Onset is often in the teenage years and prevalence peaks in the fourth decade and then declines. Tension-type headache is more common in females.[3] The infrequent subtype of TTH has scarce impact on individual and does not command much medical attention. Most headaches in patients with episodic TTH are mild to moderate and the patients can often self-manage by using simple analgesics. Results of a survey of 1573 adults, 15 years of age or above indicated that 90% of tension-type headache sufferers take over-the-counter drugs and that 55% do not consult a docto.r.[4]

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory properties. Naproxen sodium is absorbed rapidly and was approved for over-the-counter use in the United States in 1994. Naproxen sodium, at a dose of 220 mg every eight to 12 hrs (daily maximum of 660 mg), is indicated for the same over-the-counter conditions as acetaminophen.[5] Benzodiazepines are commonly used for the treatment of TTH[6-8], however, there are very few randomized controlled trials recommending the use of these drugs.[9] Extensive literature search revealed that etizolam, a newer benzodiazepines, is an effective alternative for the treatment of ETTH.[9]Etizolam is a thienodiazepine

derivative,which is a short-acting and ultra-rapidly eliminated benzodiazepine[10] and the only approved benzodiazepine for administration to TTH patients. The aim of this study was to evaluate the safety and efficacy of etizolam combined with an NSAID in an acute treatment for ETTH.

MATERIALS AND METHODS

Study Design: This prospective open label randomized study was conducted among patients visiting the Outpatient Department of Neurology, Christian Medical College and Hospital, Ludhiana. We enrolled 60 patients of episodic tension type headache, diagnosed as per International Headache Society (IHS) - II Criteria.[11]

Patients

Patients fulfilling the diagnosis of TTH as classified under ICHD-II criteria and TTH patients were diagnosed with ETTH, Patients of both sexes between the ages of 18 - 65 years were included in the study. The study plan was approved by the Institutional Ethics Committee.

Exclusion Criteria

- Patients experiencing other headaches episodes age at onset of tension-type headache of 50 years or over, patient requiring the use of following medication NSAIDs,muscle relaxants,opioids,antidepressants, hypnotics, anasthetics, antiepileptics, sedatives, antirheumatic, anti-inflammatory, antihistaminics for any medical condition were excluded,
- Patients on prophylactic medication for any other headache disorder, Pregnant and lactating women, Clinical history suggesting any peptic ulcer disease or increased bleeding tendency and Patients with history of hypersensitivity to benzodiazepines and other anti-inflammatory drugs were also excluded.

Clinical Measurement and Safety Assessment

Primary Outcome Measures was Changes in VAS (Pain free rate at 2 hr).

Secondary Outcome Measures was changes in 4 point verbal functional impairment scale, Changes in the frequency of headache and reported adverse effects

METHODOLOGY

Patients were randomly divided into two groups A and B, using computer generated random numbers. Group A (n=30) patients received NSAID alone (Naproxen 250mg).Group B

(n=30) patients received NSAIDs -Naproxen 250 mg plus etizolam 0.5mg. Patients were instructed to ingest the above medication only after experiencing an acute attack of ETTH, of at least moderate severity. They were also instructed to record the date and time of onset of headache, time of ingestion of medication, pain relief after treatment in diary. Pain intensity was recorded on a VAS scale before and after 2hr of medication. No other medication of any kind was taken concurrently with the study medication. Patients were enrolled in the study after signing the written informed consent form and the Patient's particulars were recorded in Performa. Patients then underwent thorough clinical examination including history, vital signs and systemic examination. History, vital signs, systemic examination and Visual Analogue Scale were assessed and recorded. A simple 4 point verbal functional impairment scale (measure of disability) was recorded at base line and at end of 2hr was noted.

Visual Analogue Scale (VAS) Patients were given and explained the Visual Analogue Scale in their local language and they were trained to mark VAS before starting the randomization. Patients were asked to mark it according to the severity of pain. The pain intensity was assessed on a 10 - point scale where 1 to 3 is defined as "mild", 4 to 7 as "moderate" and 8 to 10 as "severe".[12]

Functional disability on a validated scale (4-point verbal rating scale)

0 = no functional impairment, 1 = can do everything albeit with difficulty", 2 = cannot do some things and 3 = cannot do anything and/or bed-bound at 2 hours and other time points after treatment.[11]

STATISTICAL METHODS

Results were analysed using students-'t' test and Chi-Square test. A p value of < 0.05 was considered as statistically significant.

RESULTS

Total 60 patients were included in the study. The mean age of the patients in both the groups was comparable (34.9±9.7yrs) in Naproxen (group A) vs. (37.±11.5yrs) in Naproxen-Etizolam (group B). Similarly, the ratio of males and females was also comparable in both the groups (17:13 in Group A vs. 16:14 in Group B). The patient is both the groups had comparable vas score at baseline (6.7 ± 1.4 Group A vs. 6.67±1.4 in Group B).

Pain intensity 20 (66.7%) experienced moderate attacks and 10(33%) experienced severe attacks in group B (Etizolam + Naproxen sodium) .While in group A (Neproxen sodium) 18(60%) experienced moderate attacks and 12(40%) experienced severe attacks.

Pain free rate at 2 hr in group A was 9 (30 %) while in group is B (Etizolam + Naproxen sodium) was 11(36.7 %.). In group A (Neproxen sodium) out of 30 patients, 19 patients had a good pain relief of more than 50% and 11 patients reported a moderate pain relief of 25-50%.While in group B (Etizolam +naproxen) out of 30 patients, 27 patients had a good pain relief of more than 50% $p>0.03$and only 3 patients reported a moderate pain relief of 25-50%. (Figure-2).

Intensity of headache - In group B after treatment 27 (90%) had mild and 3(10%) had only moderate intensity while in group A 19(63.4%) had mild intensity of headache and 11(33.5%) had moderate intensity.(Figure -2)

The VAS for headache decreased from 6.67±1.37 to1.54±1.48 in the Naproxen-ET group ($p<0.01$), and from 6.76±1.4 to 2.6 ±2 in the Naproxen group after 2hr of medication.
(Figure-1)

All treated headache episodes daily activities were rated no more difficult than normal as early 2hr after dosing in 70 % ($p<0.05$) of headaches and 30% with albeit difficulty treated with etizolam and naproxen sodium group(B). These results were superior to corresponding results with Naproxen sodium only group (57 % normal, 13% can do albeit with difficulty 30% can do something and 1% cannot do anything at 2 hr) after taking the medication $p<0.05$%.(Table)

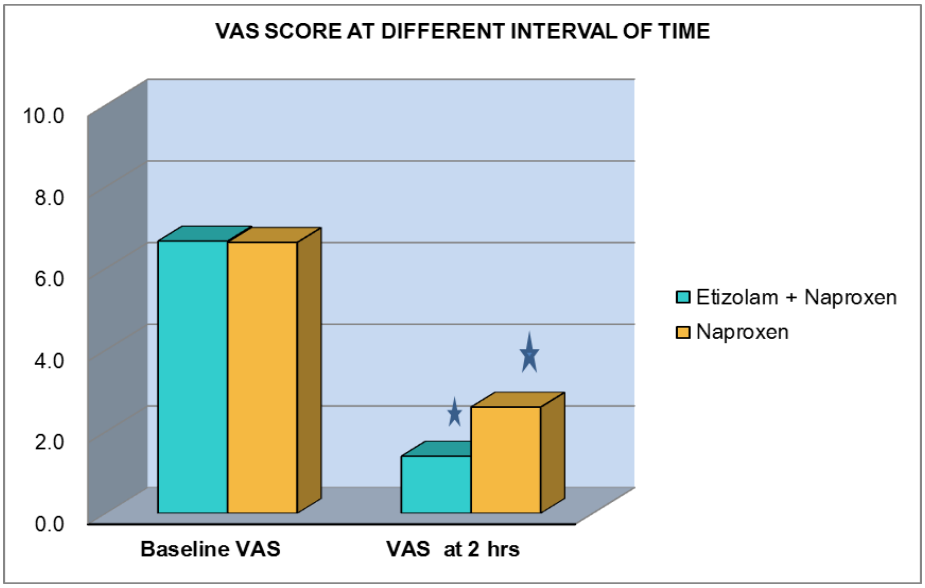
Table 1: Demographic and Baseline Characteristics of Patients In Both Groups At Baseline And After Treatment.

	NSAID+ ETIZOLAM (N=30)	NSAID (N=30)
Age	36.7 ±11.6	34.9±9.7
Sex (F:M)	16:14	17:13
2hr Pain Free Rate	36.5%	30%
Vas For Headache Intensity Before	6.67±1.4	6.76 ± 1.4
After	1.53±1.48 *	3.10 ± 1.4 *
Frequency of Headache Before Teatment	4.97±1.4	5.2 ±1.2
After Teatment	4.5 .±1.5	4.8±1.1

Table 2: Verbal rating scale

VRS at baseline	Etizolam+ Naproxen sodium	Naproxen sodium
	No of patients (%)	No of patients (%)
0	0 (0)	0 (0)
1	4 (13)	8 (27)
2	22 (74)	18 (60)
3	4 (13)	4 (13)
VRS at 2hr		
0	21 (70)*	17 (57)*
1	9 (30)	4 (13)
2	0 (0)	8 (27)
3	0 (0)	1 (3)

P <0.05 is significant. 0 = no functional impairment, 1 = can do everything albeit with difficulty", 2 = cannot do some things and 3 = cannot do anything and/or bed-bound at 2 hours.



***P<0.05**

Figure 1: Changes In Visual Analogue Scale In Both The Groups At Baseline And After Treatment.

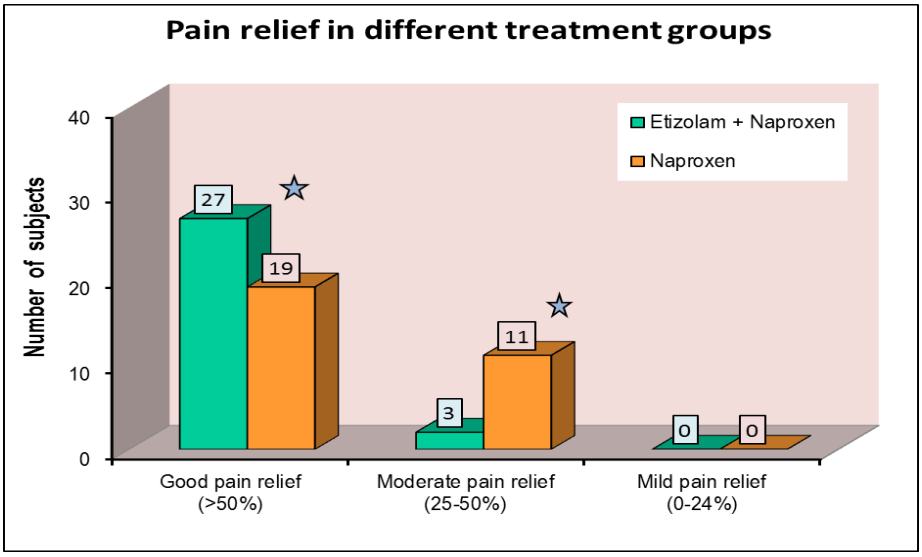


Figure 2.

Table 3

Incidence of adverse effects		
Adverse effects	**Naproxen n(%)**	**Etizolam+Naproxen n(%)**
Sleepiness	**0**	**3(10)**
Dizziness	**1(3)**	**1(3)**
Nausea	**1(3)**	**0**
Epigastric pain	**1**	**0**

DISCUSSION

Tension-type headache (TTH) is the most prevalent headache type and One with the highest socioeconomic costs.[13] The most commonly used evidence-based acute treatment for management of TTH is with NSAIDs.The Non-steroidal anti-inflammatory drugs (NSAIDs); ibuprofen, naproxen sodium, ketoprofen and diclofenac potassium, all have been demonstrated more effective than placebo in acute TTH. Most, but not all, comparative studies report that these NSAIDs are more effective than acetaminophen and aspirin.[14-15]

A correct diagnosis was assured by means of a headache diary recorded over 4 weeks[16] Identification of a high intake of analgesics is essential as other treatments are largely ineffective in the presence of medication overuse. Physicians should be aware of the risk of developing medication-overuse headache as a result of frequent and excessive use of analgesics in acute therapy.

Benzodiazepines a used for TTH treatment, address both the central and peripheral mechanisms responsible for headache.[17-20] The efficacy of the alprazolam has been confirmed for chronic TTH.[21] In addition, a combination of a long-term protocol of regular exercise, stretching, balanced meals and adequate sleep should be part of a headache treatment program .Diazepam is reported to produce the best long-term results in reducing muscle tension and relief of pain complaints, in chronic anxiety patients.[22]

In this study, we evaluated the analgesic adjuvant activity of etizolam in combination with naproxen sodium. In the present study, women were affected more than men. 53.3 % female, 46.7 % male. Boggards and terKuile reported in their meta-analysis that 78% of the general population is reported to have experienced a TTH during their lifetime, and the TTH is reported by women (88%) than by men (69%).[3]

In the present study, combination of naproxen sodium 250 mg and etizolam 0.5 mg were shown to be statistically superior to Naproxen sodium for all predefined analgesic efficacy endpoints (pain free rate in 2hrs, decrease in intensity of headache as depicted by decrease in vas score in the treatment of episodic tension-type headaches).

The guidelines for drug trials in TTH from the International Headache Society recommend pain-free after 2 h as the primary efficacy measure.[20] This has been used only in few studies

whilst many studies have used other efficacy measures such as pain intensity difference, time to meaningful pain relief which made comparison of results between studies difficult.

The combination of etizolam and naproxen sodium were effective in decreasing the intensity of headache ($p<0.05$) as compared to baseline (figure 1).

We also evaluated the pain free rate in 2hrs. The percentage of subjects with headaches completely resolved (reduced to none) at two hours was 36.7% for the combination of naproxen sodium and etizolam group, 30% for the naproxen sodium only group. These results were in proportion to study showing number of patients that were pain-free 2 hours after treatment with naproxen 375mg and placebo were 32% and 26%, respectively (Prior et al 2002).The combination of therapy was significantly more effective in reducing good pain relief (>50%) in 90% of patients than naproxen only group 63% of patients.Neproxen sodium is effective in reducing moderate pain relief (25-50%) $P< 0.05$(Figure 2).

We observed some side effects from etizolam (sleepiness or fatigue in 9.2% of patients of the NSAID-ET group), no patient dropped out due to a side effect. This result suggests that etizolam in combination with NSAIDs is well tolerated for treatment of ETTH. Patients in both the NSAID and NSAID-ET groups showed significant decreases in VAS for headache and VRS .The present study indicates that combination treatment with NSAID and etizolam is useful in treatment of episodic tension type of headache.

Hence, low dose add on etizolam to naproxen sodium therapy was very effective in improving VAS score and verbal rating scale in patients of episodic tension type of headache. Low dose add on etizolam therapy did not decreased frequency of headache. These results are in agreement with earlier studies which demonstrated a statistically significant improvement in the VAS score and nearly all secondary efficacy measures, Frequency of headache and 4 point verbal rating scale was not assessed in earlier studies.

The vas score indicate that add on low-dose etizolam therapy was more effective in improving headache severity as compared to conventional therapy. There was no serious adverse event reported in both the groups. The most common adverse effects reported in our study with add on etizolam therapy was sleepiness, whereas in the neproxen sodium group patients reported with nausea and epigastric pain. No patient was lost to the follow-up. (Table 3)

In conclusion, add-on therapy with etizolam on naproxen sodium had earlier onset of action, better efficacy as compared to naproxen sodium alone in episodic tension type of headache in Indian patients.

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