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An investigantional clinical evaluation of efficacy of milnacipran compared with sodium oxybate in patients suffering with fibromyalgia

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ABSTRACT

Fibromyalgia is a disorder characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory and mood issues. Although fibromyalgia is often considered an arthritis-related condition, it is not truly a form of arthritis (a disease of the joints) because it does not cause inflammation or damage to the joints, muscles, or other tissues. The aim of the study is to find the efficacy of the investigational product compared with sodium oxybate in patients suffering with fibromyalgia. The objective of the study is to study the quality of life of patients suffering with fibromyalgia to observe the therapeutic efficacy of the drug, and compare with the reference drug to record the adverse events if reported to present the thesis which increase and deepen knowledge of the life situation of subjects suffering with fibromyalgia. Disturbed sleep has a major impact on quality of life and is often a common symptom of many other chronic conditions, such as chronic pain and mood disorders. The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. The improvements reflected in Version 2.0 of the SF-36; psychometric studies of assumptions underlying scale construction and scoring; how they have been translated in more than 50 countries as part of the International Quality of Life Assessment (IQOLA) Project; and studies of reliability and validity. Milnacipran 100mg once daily has a predominantly analgesic effect as evidenced by the significant clinical benefits. Higher dose was associated with higher pain reduction. The results from the study show that milnacipran led to statistically significant improvements in pain and other multiple symptoms of FM.

INTRODUCTION

Like arthritis, however, fibromyalgia can cause significant pain and fatigue, and it can interfere with a person's ability to carry on daily activities [1]. Also like arthritis, fibromyalgia is considered a rheumatic condition, a medical condition that impairs the joints and/or soft tissues and causes chronic pain. Researchers believe that fibromyalgia

amplifies painful sensations by affecting the way your brain processes pain signals [2]. The exact cause of fibromyalgia is unknown, but it's thought to be related to abnormal levels of certain chemicals in the brain and changes in the way the central nervous system (brain, spinal cord and nerves) processes pain messages carried around the body [3-8].It typically presents in young or middle-aged women but can affect patients of either sex and at any age. Fibromyalgia is a disorder characterized by widespread musculoskeletal pain accompanied by fatigue, sleep, memory and mood issues [9]. Researchers believe that fibromyalgia amplifies painful sensations by affecting the way your brain processes pain signals. Symptoms sometimes begin after a physical trauma, surgery, infection or significant psychological stress. In other cases, symptoms gradually accumulate over time with no single triggering event [10]. Women are much more likely to develop fibromyalgia than are men. Many people who have fibromyalgia also have tension headaches, temporomandibular joint (TMJ) disorders, irritable bowel syndrome, anxiety and depression. While there is no cure for fibromyalgia, a variety of medications can help control symptoms. Exercise, relaxation and stress-reduction measures also may help [11]. For unknown reasons, between 80 and 90 percent of those diagnosed with fibromyalgia are women; however, men and children also can be affected [12-15]. Most people are diagnosed during middle age, although the symptoms often become present earlier in life. Fibromyalgia affects more than 3.7 million Americans, the majority of whom are women between the ages of 40 and 75, but it also affects men, young women and children [16]. People with other rheumatic diseases, such as rheumatoid arthritis or lupus, are at greater risk for fibromyalgia. For example, about 20 to 30 percent of people with rheumatoid arthritis also develop fibromyalgia, although no one knows why. Women who are overweight or inactive have an increased risk of developing fibromyalgia [17]. Fibromyalgia sometimes occurs in more than one member of the same family, but doctors have not verified a hereditary link or common genetic type. Several studies have, however, found a possible link between genetic markers called human leukocyte antigens, or HLAs, and fibromyalgia [18]. This suggests that a gene that predisposes a person to develop fibromyalgia may exist. Although fibromyalgia is more common in adults, children (especially adolescent females) may be diagnosed with fibromyalgia.

The aim of the study is to find the efficacy of the investigational product compared with sodium oxybate in patients suffering with fibromyalgia. The objective of the study is to study the quality of life of patients suffering with fibromyalgia to observe the therapeutic efficacy of the drug, and compare with the reference drug to record the adverse events if reported and to present the thesis which increase and deepen knowledge of the life situation of subjects suffering with fibromyalgia.

MATERIALS AND METHODS

MOS Sleep Scale

Intended to assess the extent of sleep problems, the MOS Sleep Scale measures six dimensions of sleep, including initiation, maintenance (e.g. staying asleep), quantity, adequacy, somnolence (e.g. drowsiness) and respiratory impairments (e.g. shortness of breath, snoring). Disturbed sleep has a major impact on quality of life and is often a common symptom of many other chronic conditions, such as chronic pain and mood disorders. The MOS Sleep Scale was originally developed in the Medical Outcomes Study (MOS), but has recently been revised. The new form, the MOS Sleep Scale–Revised (MOS Sleep–R), differs from the original in that it has five response options, rather than six, for each question. The response option "a good bit of the time" has been eliminated. This change was made based on findings from SF-36® Health Survey translation studies (Keller, Ware, Gandek et al., 1998), that this response choice was not consistently ordered in relation to other adjacent response choices ("most of the time" and "some of the time"). Eliminating this response option simplified the format of the form with little or no loss of information [19]. The reliability and validity of the MOS Sleep Scale have been evaluated in a number of disease areas, including neuropathic pain, restless leg syndrome, overactive bladder and rheumatoid arthritis. It has also been evaluated in the U.S. general population. Starting in 2010, the MOS Sleep Scale is available with patient and aggregate reports and a single standardized scoring engine. Updated U.S. norms are also available using 2009 survey results.

SF-36 PHYSICAL AND MENTAL COMPONENTS

The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments [20]. This book chapter summarizes the steps in the construction of the SF-36; how it led to the development of an even shorter (1-page, 2-minute) survey form -- the SF-12; the improvements reflected in Version 2.0 of the SF-36; psychometric studies of assumptions underlying scale construction and scoring; how they have been translated in more than 50 countries as part of the International Quality of Life Assessment (IQOLA) Project; and studies of reliability and validity.

ASSESSMENT OF VAS

Description

VISUAL ANALOG SCALE (VAS) is a one-dimensional measure of pain intensity (1), which has been widely used in diverse adult populations, including those with osteoarthritis.

Content

The pain VAS is a continuous scale comprised of a horizontal (HVAS) or vertical (VVAS) line, usually 10 centimeters (100 mm) in length, anchored by 2 verbal descriptors, one for each symptom extreme . Instructions, time period for reporting, and verbal descriptor anchors have varied widely in the literature depending on intended use of the scale.

Number of items

The pain VAS is a single-item scale.

Method of administration

The pain VAS is self-completed by the respondent. The respondent is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity.

Scoring

Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the “no pain” anchor and the patient’s mark, providing a range of scores from 0–100.

Score interpretation

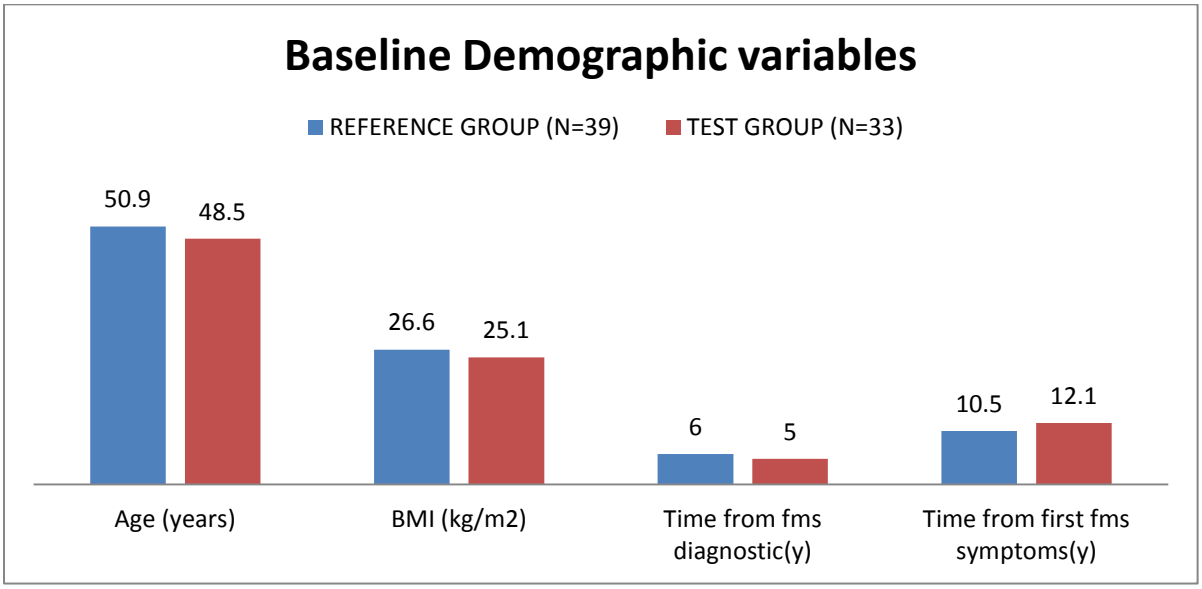
A higher score indicates greater pain intensity. Based on the distribution of pain VAS scores in postsurgical patients (knee replacement, hysterectomy, or laparoscopic myomectomy) who described their postoperative pain intensity as none, mild, moderate, or severe, the following cut points on the pain VAS have been recommended: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75– 100 mm) (11). Normative values are not available.

RESULTS AND DISCUSSION

Total 100 patients were enrolled in the study conducted at PRIME HOSPITALS, AMEERPET. Out of 100 subjects, 50 were randomized into test group and 50 were randomized into reference group. All subjects were given information about the study, and the benefits of the study. 11 subjects from the reference group were dropped out from the study due to lack of interest, lack of efficacy. 17 subjects from test group were withdrawn from study. Total 39 in reference group and 33 from test group were enrolled. The inform consent was taken from the them. The base line demographic characteristics like age, BMI, and time from FMS symptoms were diadnosed were collected in the case report form, for both groups, the response was taken and the mean was presented for each group. This is in the table no 1, and represented in graph no 1. Family history was also collected from the subjects, 10 subjects from reference had family history if FMS, that is 26%, and 29 (74%) subjects had no family history. In test group 16 (42%) subjects had family history of FMS, where 22(58%) subjects did not had any family history this is charted in table no 2, plotted in graph no 2. Table no 3 represents the number of subjects with tender points at screening and weekly recall pain vas was presented, and plotted in graph no 3. Table no 4 represents the treatments taken by patients before the study; it was taken at screening on the day before the treatment was started.

Table No 1- Baseline Demographic Characteristics at Screening

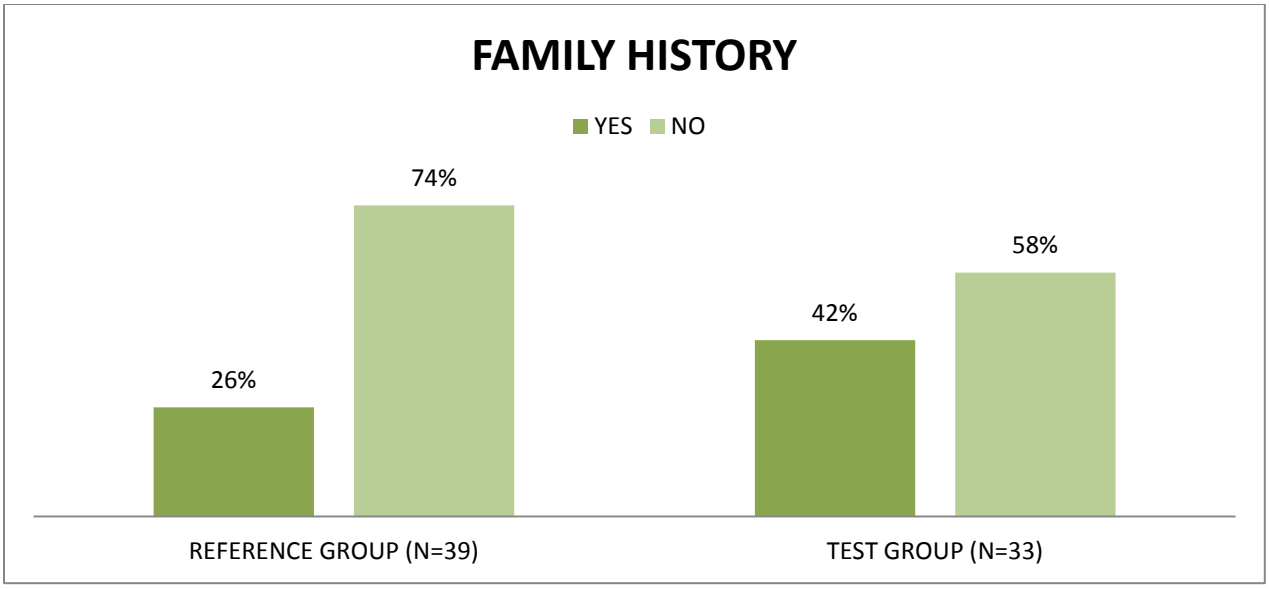
Baseline demographic characteristics	REFERENCE GROUP(N=39)	TEST GROUP(N=33)
Age(years)	50.9(11.4)	48.5(11.4)
BMI(kg/m2)	26.6(5.2)	25.1(4.2)
Time from fms diagnostic(y)	6.0(5.0)	5.0(4.7)
Time from first fms symptoms(y)	10.5(7.7)	12.1(9.2)



Graph No 1: Baseline Demographic Characteristics at Screening

Table No 2- Family History

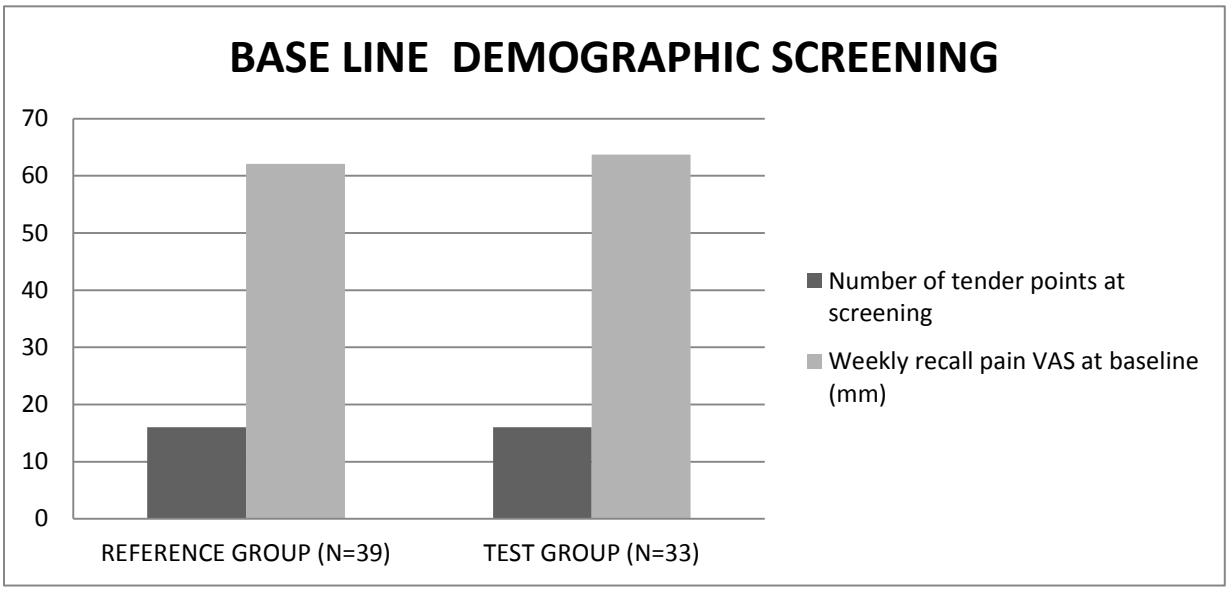
Family history of fms	Reference group (n=39)	Test group(n=33)
Yes	10(26%)	16(42%)
No	29(74%)	22(58%)



Graph No 2- Family History

Table No 3- Baseline Demographic Screening

Baseline characteristics	Reference group (n=39)	Test group(n=33)
Number of tender points at screening	16.0(2.0)	16.0(1.4)
Weekly recall pain VAS at baseline (mm)	62.1(14.5)	63.7(15.1)

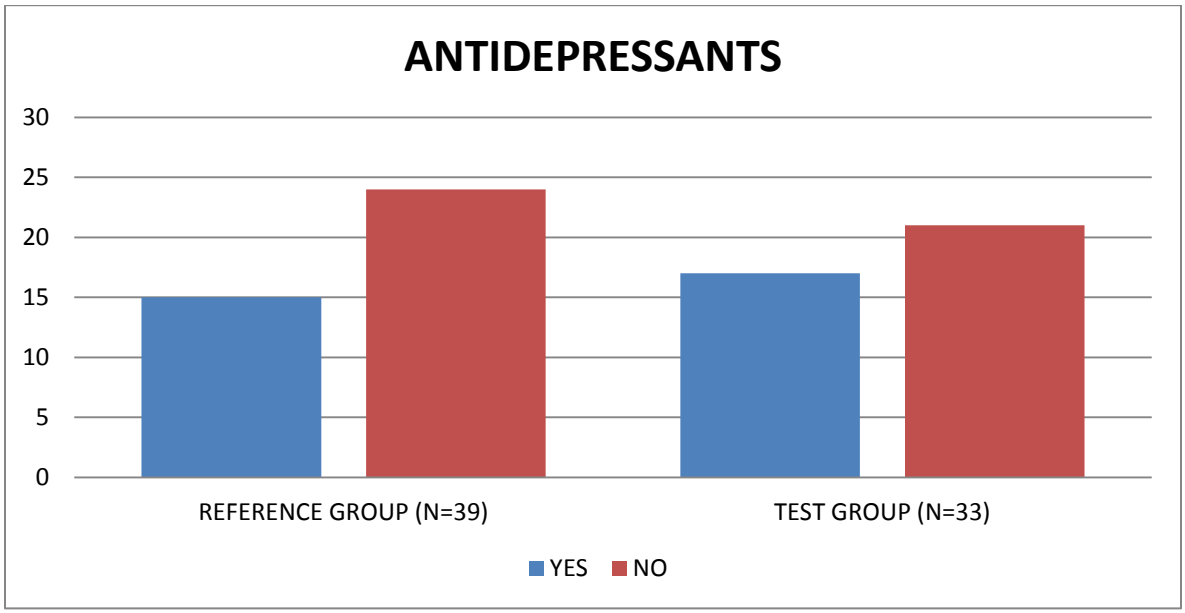


Graph No 3- Baseline Demographic Screening

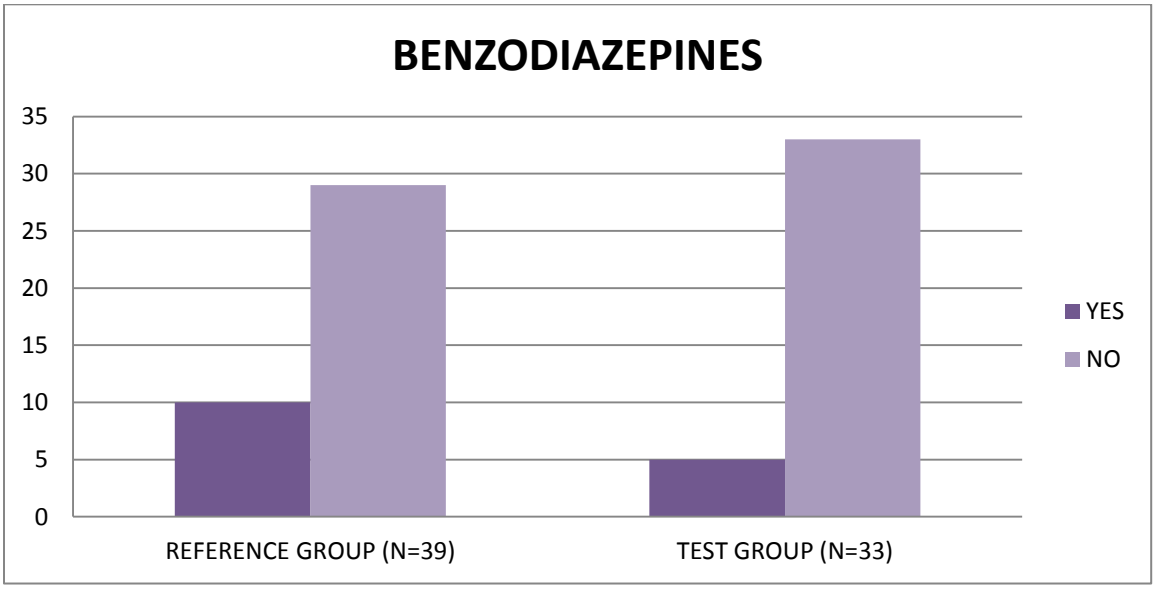
Table 4- Analgesic Treatment at Screening

Analgesic treatment at screening	Reference group (n=39)	Test group(n=33)
Antidepressants		
Yes	15(39%)	17(45%)
No	24(61%)	21(55%)

Other analgesics		
Yes	26(67%)	27(71%)
No	13(33%)	11(29%)
Benzodiazepines		
Yes	10(25%)	5(13%)
No	29(75%)	33(87%)



Graph No 4- Analgesic Treatment at Screening

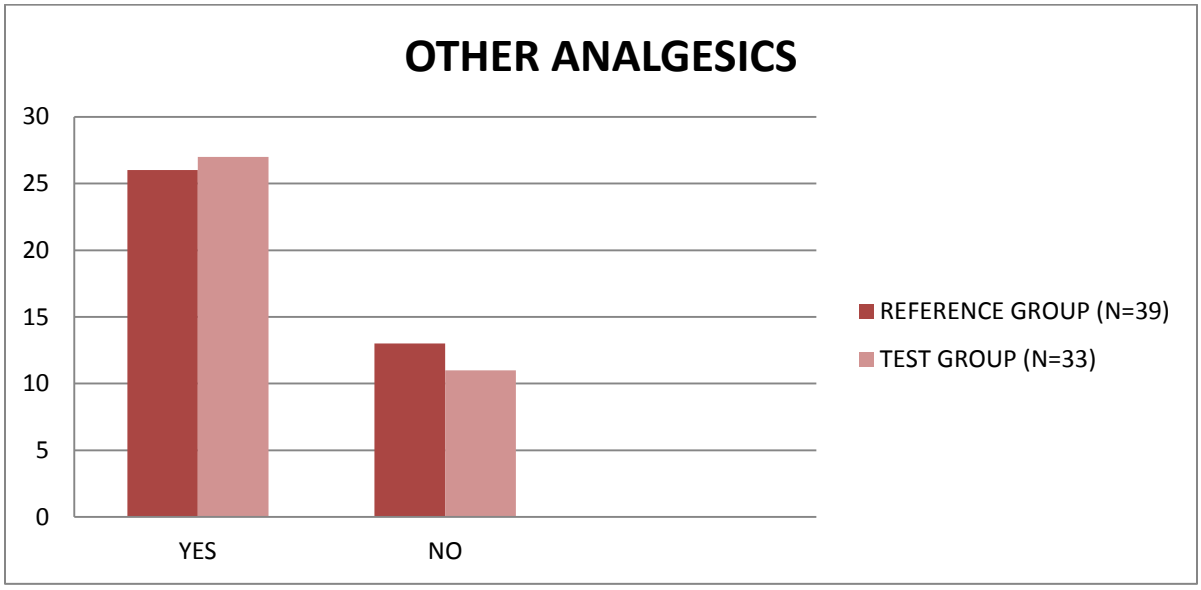


Graph No 4.1- Analgesic Treatment at Screening Benzodiazepines

Table No.5: Screening

BASELINE DAY-0	REFERENCE GROUP (N=39)	TEST GROUP (N=33)
WRP VAS (mm)	62.1(14.5)	63.7(15.1)
CP VAS (mm)	50.8(21.8)	46.8(18.7)

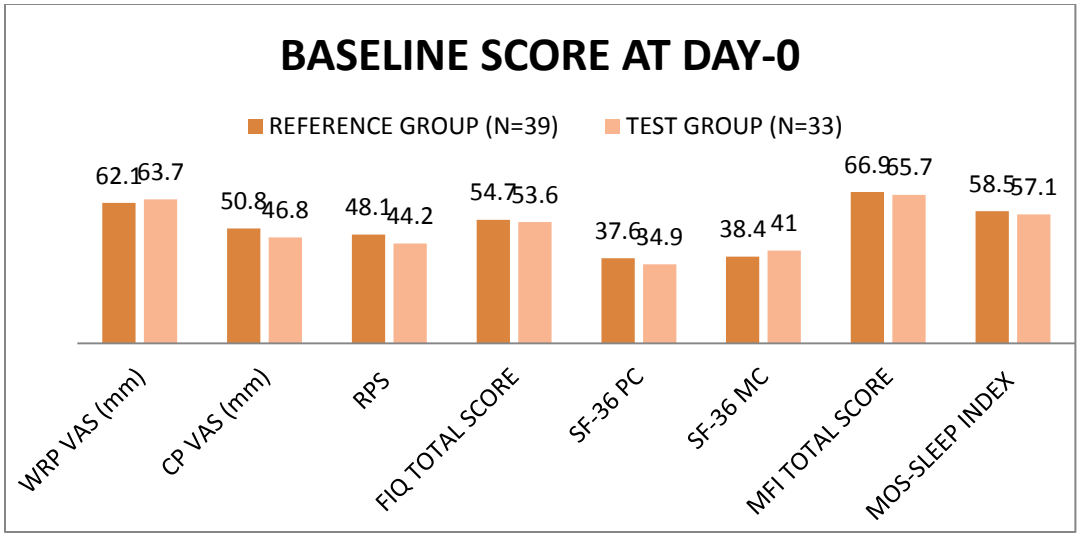
RPS	48.1(17.1)	44.2(17.1)
FIQ TOTAL SCORE	54.7(14.4)	53.6(17.0)
SF-36 PC	37.6(6.9)	34.9(7.5)
SF-36 MC	38.4(9.6)	41.0(9.7)
MFI TOTAL SCORE	66.9(13.6)	65.7(11.7)
MOS-SLEEP INDEX	58.5(17.9)	57.1(18.1)



Graph No 5- Analgesic Treatment at

Table No 6 - Baseline Vas Score before Treatment

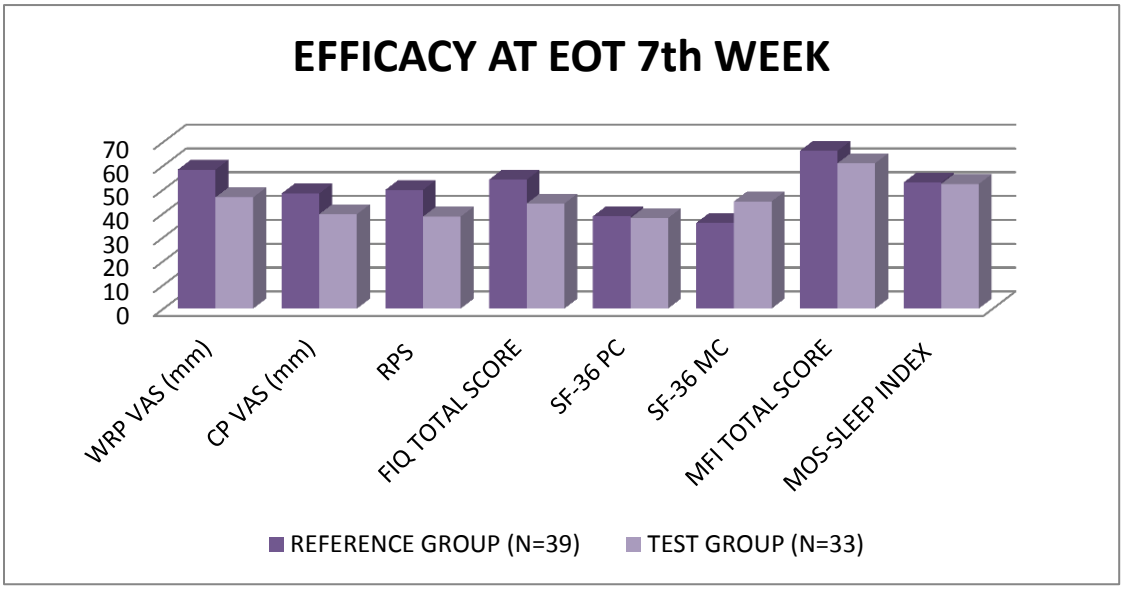
BASELINE DAY-0	REFERENCE GROUP (N=39)	TEST GROUP (N=33)
WRP VAS (mm)	62.1(14.5)	63.7(15.1)
CP VAS (mm)	50.8(21.8)	46.8(18.7)
RPS	48.1(17.1)	44.2(17.1)
FIQ TOTAL SCORE	54.7(14.4)	53.6(17.0)
SF-36 PC	37.6(6.9)	34.9(7.5)
SF-36 MC	38.4(9.6)	41.0(9.7)
MFI TOTAL SCORE	66.9(13.6)	65.7(11.7)
MOS-SLEEP INDEX	58.5(17.9)	57.1(18.1)



Graph No 6 - Baseline Vas Score before Treatment

Table 7- Efficacy at The 7th Week Eot

EFFICACY OF EOT	REFERENCE GROUP (N=39)	TEST GROUP (N=33)
WRP VAS (mm)	58.3 (24.6)	46.7 (26.3)
CP VAS (mm)	48.3 (25.1)	39.6 (23.1)
RPS	49.8 (19.5)	38.6 (19.5)
FIQ TOTAL SCORE	54.1 (18.6)	44.1 (20.8)
SF-36 PC	38.7 (7.3)	38.0 (7.7)
SF-36 MC	36.0 (10.4)	45.0 (11.9)
MFI TOTAL SCORE	66.2 (15.5)	61.0 (15.9)
MOS-SLEEP INDEX	52.9 (19.8)	52.3 (19.0)



Graph No 7- Efficacy at The 7th Week Eot

DISCUSSION

The inform consent was taken from them. The base line demographic characteristics like age, BMI, and time from FMS symptoms were diagnosed were collected in the case report form, for both groups, the response was taken and the mean was presented for each group. This is in the table no 1, and represented in graph no 1. Family history was also collected from the subjects, 10 subjects from reference had family history if FMS, that is 26%, and 29 (74%) subjects had no family history. In test group 16 (42%) subjects had family history of FMS, where 22(58%) subjects did not had any family history this is charted in table no 2, plotted in graph no 2. Table no 3 represents the number of subjects with tender points at screening and weekly recall pain vas was presented, and plotted in graph no 3. Table no 4 represents the treatments taken by patients before the study; it was taken at screening on the day before the treatment was started. There were 39% subjects used antidepressants in reference group and 45 % in test group, benzodiazepines were also used by subjects 25% in the reference group and 13% in the test group, the survey shows that subjects were more dependent on other analgesics when compared to antidepressants and benzodiazepines [22-24]. There were 67% subjects were used other analgesics and 71% in test group. This is presented in the graph no 4, 5, and 6. Table 5 presents the baseline demographic response before the treatment was started on day -0, the treatment was for 7 weeks, presented in graph no 7 The subjects were asked to take the treatment every day for 7 weeks. Table 6 represents the efficacy of the drug treatments after 7 weeks. That is the end of the treatment, plotted in graph no 8. Both drug treatments effective in subjects. Both groups responded to the drug for the period of 7 weeks. There was significant response in the test group compared with the reference. The efficacy was measured by WRPS VAS, CP VAS, RPS, FIQ SCORE, AND SLEEP INDEX. The test group has reduced its score in vas than the reference group. By the results it can be said that the test drug has greater efficacy than the reference group. The purpose of the study was to evaluate the efficacy of the drug milnacipran compared with sodium oxybate. Milnacipran 100mg once daily has a predominantly analgesic effect as evidenced by the significant clinical benefits. Higher dose was associated with higher pain reduction. The results from the study show that milnacipran led to statistically significant improvements in pain and other multiple symptoms of FM.

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