

**Research Article**

A Comparative Study in Patients with Fibromyalgia Receiving Probiotics Along with Standard Therapy

Authors

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Abstract

Background: *The present study was done to determine the impact of gut microbiome in altering the symptoms of fibromyalgia..*

Aim: *To study the benefits of adding probiotics along with standard therapy in fibromyalgia.*

Materials and Methods: *A total of 104 patients aged 20-65 were included in this study. The patients were divided into two groups, Case (N=52) and Control (N=52). The Case group received Bacillus subtilis probiotic (10 billion CFU's) along with Amitriptyline (10mg), whereas the Control group received Amitriptyline alone (10mg). The patients were evaluated 14 days after baseline, and then monthly for six months. Assessment of patients was done with the help of the Visual Analog Scale (VAS) and the Revised Fibromyalgia Impact Questionnaire (FIQR).*

Results: *Significant improvement was observed in both groups after ten weeks of treatment ($p < 0.05$). Percentage reduction in VAS –Pain score, FIQR-Pain score, and the FIQR- Total score was slightly higher in the case group compared to that of control (difference of approximately 2%). However, the percentage reduction in the FIQR-Sleep quality score showed a greater improvement in the Case group to that of control (difference of approximately 23%).*

Conclusion: *Both groups showed significant improvement in pain, functional status and neuropsychological symptoms; however, the addition of probiotics as an adjuvant to standard therapy showed additional improvement in pain, functional status, and sleep quality. Consequently, based on results obtained, probiotics can be used as an adjuvant in the management of Fibromyalgia.*

Keywords: *Fibromyalgia, amitriptyline, probiotics, Bacillus subtilis.*

Introduction

Fibromyalgia is a condition resulting in excessive somatic hyperalgesia, allodynia and neuropsychological symptoms. It typically presents in women, but can affect patients of either sex and at any age. Fibromyalgia is characterized mainly by widespread pain, decreased pain threshold, and characteristic

symptoms including non-restorative sleep, fatigue, stiffness, mood disturbances, headache, and other less common features⁽¹⁾. People with Fibromyalgia have reduced delta sleep. The deprivation of delta sleep produces the signs and symptoms of fibromyalgia, supporting it as a non - restorative sleep disorder⁽²⁾. In almost all patients, impairment of central pain mechanism, neuroendocrinological

abnormalities, and abnormal activation in the nociceptive domain of the brain are seen⁽³⁾. Several medications like Amitriptyline, Pregabalin, Duloxetine, and Milnacipran is being used for treating fibromyalgia. But these pharmacological effect have a very limited to moderate effect on reducing chronic pain among people with fibromyalgia⁽¹⁾. Excessive lipopolysaccharides stimulation due to bacterial dysbiosis, small intestinal bacterial growth or increased intestinal permeability may produce systemic and central nervous system inflammation.

Bacterial enzymes may produce neurotoxic metabolites such as D-Lactic acid and ammonia.⁽⁶⁾ Bacterial proteins may cross-react with human antigens to stimulate the dysfunctional response of the adaptive immune system⁽⁷⁾. Probiotics influence the impact of the gut micro biome on the CNS and have shown significant effects on brain function.⁽⁵⁾ Probiotics are live microorganisms that when administered in adequate amounts grants a health benefit on the host. Most of the organisms used and marketed as probiotics belong to the genera Lactobacillus, Escherichia, Enterococcus, Bacillus, Streptococcus and Bifidobacterium. The subtypes of these strains are found in the Human Gut Micro biome⁽⁴⁾. Communication between the CNS and ENS is mediated by the Gut-Brain Axis. Effect of probiotics on various mediators of the brain-gut axis has been demonstrated.⁽⁸⁾⁽¹⁰⁾

It is believed that the microbiota, as well as probiotics, can have a significant impact on the gut-brain axis, but further research in this area is needed to reveal the magnitude, mechanisms and clinical relevance of these effects⁽⁹⁾. The human gut bacteria alter the neuronal circuitry by direct microbial effects on the ENS, with CNS transmission through vagal nerve. The gut microbes can produce hormones and neurotransmitters that are identical to those produced by humans. Through these varied mechanisms these gut microbes influence the architecture of sleep, memory, mood, and cognition. They are clinically and therapeutically

relevant to a range of disorders like chronic fatigue syndrome, fibromyalgia and restless leg syndrome⁽⁵⁾

FIQR is the most commonly used instrument in the evaluation of FM patients developed in 2008. It consists of 21 questions divided in to 3 domains (function, overall impact and symptoms. All questions are graded on a 0-10 numeric scale. Domain one consists of 9 questions based on physical function in which the sub-total is divided by 3. Domain two consists of 2 questions based on overall impact of FM in their life in which the sub-total is left unchanged. Domain three consists of 10 questions based on FM symptoms in which the sub-total is divided by 2. The sub-total from the three domains are added to get the FIQR total score which ranges between 0-100.⁽¹¹⁾

Objectives

To assess the benefits of probiotics in the management of fibromyalgia based on

- Improvement in Pain (measured by validated pain assessment-Visual Analog Scale).
- Improvement in functional status (using Revised Fibromyalgia Impact Questionnaire)
- Improvement in Sleep Quality (using Revised Fibromyalgia Impact Questionnaire).

Materials and Methods

This was a prospective single blinded observational study conducted in the Neurology department of a 650 bedded tertiary care teaching hospital over a period of 6 months from November 2017 to April 2018. From the 195 patients who visited the Neurology department, 104 patients who satisfied the inclusion, as well as exclusion criteria, were allotted to study. Significant approval from the Institutional Ethical Committee for the study was obtained from the Institutional Ethics Committee of National College of Pharmacy, manassery (NCP/IEC/2017/No.086). Patients were selected based on the inclusion and exclusion criteria based on their subjective and objective evidence.

Inclusion Criteria

- All patients are having a clinical diagnosis

of Fibromyalgia.

- Patients between age 20 and 65years.
- Patients who are on amitriptyline treatment.

Exclusion Criteria

- The patient below the age of 20years.
- Pregnant Women and lactating mothers.
- Patients with comorbidities like DM (5 years), peripheral neuropathy and seizure disorders on treatment.

The patients were randomly arranged into case group and control group where, case group received probiotics bacillus subtilis (10 million CFU’s)-1teaspoon OD along with standard treatment (amitriptyline) while control group received only amitriptyline. The sample populations were requested to answer the questionnaire form at the time of their first review, and relevant information’s were collected. Initial assessment is done in 14 days from base line and subsequent assessment will be done on every month for a period of 6 months

The collected data were analysed and compared to assess the effect of probiotics in (1): Pain (using Validated Pain Assessment Scale) (2): Functional status (using Revised Fibromyalgia Impact Questionnaire) (3): Sleep Quality (using Revised Fibromyalgia Impact Questionnaire)

Statistics

The data entry and statistical analysis were done using software SPSS version (17). A p value of < 0.05 was considered to be statistically significant.

Results

Based on Age

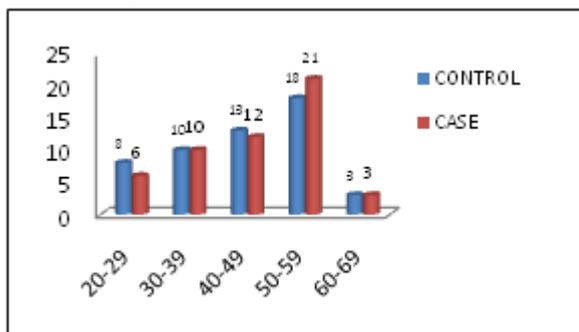


Figure 1: Distribution based on age

The age wise distribution shown in the figure describes that high frequency of subjects were in

between 50-59(37.5%) followed by 40-49(24.03%), 30-39(19.23%), 20-29(13.46%) and 60-69 (5.76%) age group.

Based on Gender

Table No 2: Distribution based on gender

	Control	Case	Total
Male	13	10	23
Female	39	42	81

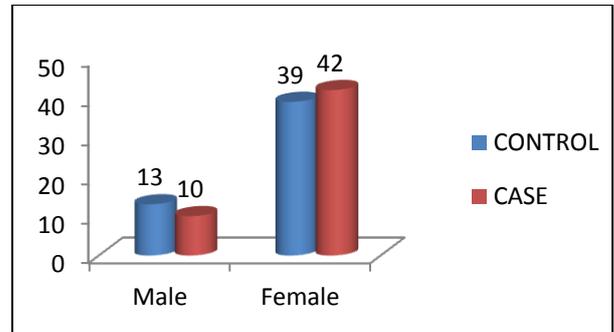


Figure No 2: Distribution based on gender

The table no.2 shows the gender wise distribution of study population. Out of total population (n=104), female patients were found to be more predominant than male patients with the prevalence rate of 77.88 % (81) and 22.1% (23) respectively. This data is shown in the figure no: 2.

Common Comorbidities Associated with FM

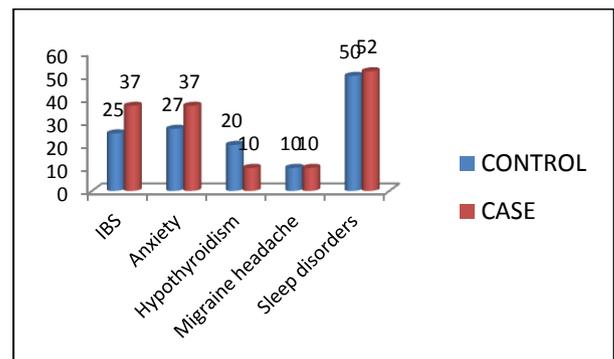


Figure No 3: Distribution based on comorbidities

From Figure no: 3, it has been observed that IBS, anxiety and sleep disorders were found to be the most prevalent comorbidities associated with FM.

**Based on Mean VAS –Score
Paired Samples Test for VAS-Score in case and control groups.**

MEAN	SD	df	P value
4.90385	.29768	51	0.000

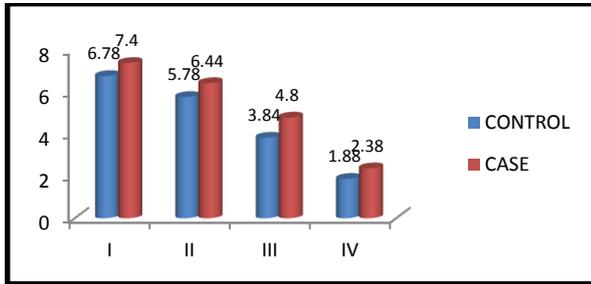


Figure No 3: Based on mean VAS –score

In the entire study population, patients in the case group showed greater percentage reduction in the VAS score (51.5%) as compared to control (49%).

- P- value of control group = 0.00
- P- value of case group = 0.00

**Based on FIQR-Pain Score
Paired Samples Test for FIQR- Pain Score in case and control groups.**

MEAN	SD	df	P value
5.01923	0.13868	51	0.000

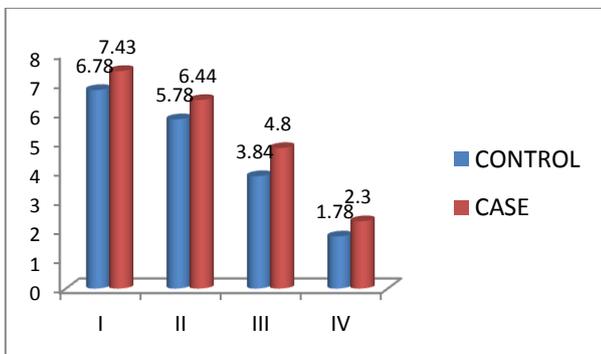


Figure No 5: Based on FIQR-Pain score

In the entire study population, patients in the case group showed greater percentage reduction in FIQR –Pain score (51.3%) as compared to control (50%).

- P- value of control group = 0.00010
- P- value of case group = 0.00026

**Based on FIQR –Total Score
Paired Samples Test for FIQR-Total Score in case and control groups.**

MEAN	SD	df	P value
3.9980	0.13868	51	0.003210

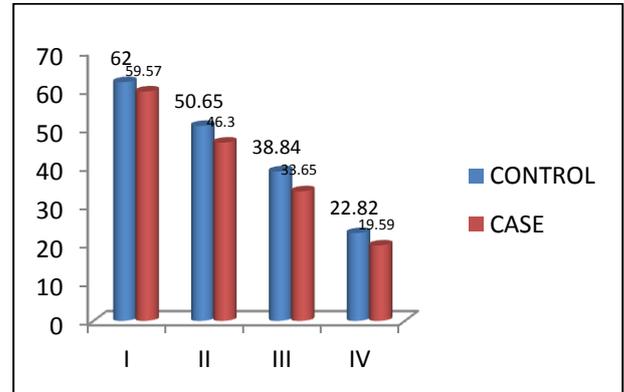


Figure No 6: Based on mean FIQR-Total score

In the entire study population, patients in the case group showed greater percentage reduction in FIQR-Total score (39.98%) as compared to control (39.18%).

- P- value of control group = 0.0130
- P- value of case group = 0.003210

**Based on FIQR-Sleep Quality Score
Paired Samples Test for FIQR-Sleep Quality Score in case and control groups.**

MEAN	SD	df	P value
5.15385	0.136432	51	0.0001

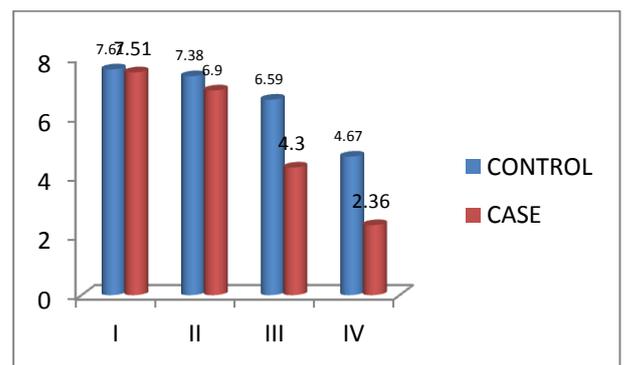


Figure No 7: Based on FIQR-Sleep quality score

In the entire study population, patients in the case group showed greater percentage reduction in FIQR – Sleep quality score (51.5%) as compared to control (27.1%).

- P- value of control group = 0.001
- P- value of case group = 0.001

Discussion

In our study, the entire study population was categorized into five age groups and most of the study population is distributed between 50 – 59 years age group. The females constituted the majority number among both case and control groups in the study. IBS, anxiety and sleep disorders were the most common comorbid conditions associated with FM.

Lin Chang. et al., 2009, the study states that patients with FM and IBS were more bothered by the somatic stimuli, leading to somatic hyperalgesia, with lower pain thresholds, higher pain frequency and severity.

Goebel A et al., June 2008 correlated altered intestinal permeability (caused due to small intestinal bacterial overgrowth (SIBO) with fibromyalgia. The study concludes that intestinal permeability was increased in fibromyalgia.

Wallace DJ et al., (2004) correlated the link between SIBO and fibromyalgia symptoms in 57 patients and came to the conclusion that small intestinal bacterial overgrowth is associated with hyperalgesia in FM.

F Wolfe et al., March 2007, investigated the association of serum serotonin with FM in 292 patients and concluded that serum serotonin levels are significantly lower in people with FM compared to those without FM. In our study, 52 patients in the case group showed a greater percentage reduction in the VAS –Pain score (50.2%) compared to that of control (49%), with a p-value of <0.05.

T Pagano. et al, 2004, study states that FM patients have a worse Quality of Life and higher levels of anxiety as compared to non- FM patients. In our 6-month study, the case group showed greater percentage reduction based on FIQR-Total Score (39.98%) compared to that of control (39.18%) with a p-value of <0.05. FIQR-Pain Score in the case group showed a greater reduction in FIQR-Pain score (51.3%) compared to that of control (50%), with p-value <0.05. Functional status was assessed using FIQR. Each patient was asked to rate the 3 FIQR domains in 0 to 10 score. Reduction of FIQR-Total score upon subsequent

reviews rates the improvement in functional status.

M.Takada. et al., 2011, the study states that the administration of probiotics (*Lactobacillus casei* Shirota) caused a significant improvement in sleep quality. In our study, case group showed significantly greater percentage reduction with respect to FIQR-Sleep quality Score (51.50%) compared to that of control (27.1%) with the p-value of <0.05. The null hypothesis (which states that the addition of probiotics will not have a benefit in the treatment of fibromyalgia symptoms) thus gets rejected, supporting the alternative hypothesis. Based on the results obtained, we conclude that probiotics, when given as an adjuvant in the management of FM along with the standard therapy, may have a beneficial effect.

Conclusion

Fibromyalgia patients who start probiotic/ amitriptyline combination therapy experience better Quality of Life and symptomatic improvement than patients on amitriptyline alone. Statistically significant beneficial effect was found on pain, functional status and sleep quality. These improvements in clinical outcomes support the use of this treatment in patients with fibromyalgia

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