Original Article

Effects of cognitive behavioral therapy in patients with fibromyalgia: a single blind, randomized controlled study

Efeitos da terapia cognitivo-comportamental em pacientes com fibromialgia: um único estudo cego, randomizado e controlado

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ABSTRACT | INTRODUCTION: Fibromyalgia (FM) is a long-lasting musculoskeletal pain, which remains a problematic clinical entity globally and the management of this condition is a challenge for the health providers. Numerous individual treatment options are available to improve the symptoms of fibromyalgia, but a specificity tailored to particular patient is still missing. Thus, in this study we tested both the individual effects of physiotherapy techniques and the combination of cognitive behavioral therapy along with physiotherapy techniques would bring any changes on the fibromyalgia symptoms. **OBJECTIVE:** To determine the combined effect of cognitive behavioral therapy along with physiotherapy techniques in the management of fibromyalgia symptoms. **METHODS:** This experimental study recruited 60 FM participants aged 18-50 years from Dehradun, India and were randomized into one of 2 groups: Integrated Physiotherapy only, integrated physiotherapy and cognitive behavioral therapy for 12 weeks. Visual analogue scale, revised fibromyalgia impact questionnaire, beck depression index, shortform-36 health surveys, Pain pressure algometer, General Anxiety Disorder - 7 were recorded at baseline, four weeks, eight weeks and twelve weeks. **RESULTS:** After three months significant improvement ($p<0.05$) were noted on all the above outcome measures of integrated physical therapy and cognitive behavioral therapy group. **CONCLUSION:** Cognitive behavioral therapy combined with Physiotherapy treatment had an effect to reduce the depression and disability, improvement on the quality of life on fibromyalgia.

KEYWORDS: Fibromyalgia. Fascial release. Cognitive Behavioral Therapy. Pain threshold.

RESUMO | INTRODUÇÃO: A fibromialgia (FM) é uma dor musculoesquelética de longa duração, que continua a ser uma entidade clínica problemática a nível mundial e a gestão desta condição é um desafio para os profissionais de saúde. Numerosas opções de tratamento individual estão disponíveis para melhorar os sintomas da fibromialgia, mas ainda falta uma especificidade sob medida para determinados pacientes. Assim, neste estudo testamos tanto os efeitos individuais das técnicas de fisioterapia quanto a combinação de terapia cognitivo-comportamental com técnicas de fisioterapia trariam alguma alteração nos sintomas da fibromialgia. **OBJETIVO:** Determinar o efeito da combinação de terapia cognitiva comportamental juntamente com técnicas de fisioterapia na gestão dos sintomas de fibromialgia. **MÉTODOS:** Este estudo experimental recrutou 60 participantes FM com idades entre 18-50 anos de Dehradun, Índia, e foram divididos aleatoriamente em 2 grupos: apenas Fisioterapia integrada e fisioterapia integrada e terapia cognitiva comportamental, durante 12 semanas. Escala analógica visual, questionário impacto fibromialgia revisado, índice de depressão Beck, versão abreviada-36 inquéritos de saúde, algômetro de pressão da dor, distúrbio de ansiedade geral - 7 foram registados na linha de base, quatro semanas, oito semanas e dose semanas. **RESULTADOS:** Após três meses, melhoras significativas ($p <0,05$) foram observadas em todas as medidas de resultados acima de fisioterapia integrada e grupo de terapia cognitivo-comportamental. **CONCLUSÃO:** A terapia cognitiva-comportamental combinada com tratamento fisioterápico teve um efeito de reduzir a depressão e a deficiência, melhorando qualidade de vida na fibromialgia.

PALAVRAS-CHAVE: Fibromialgia. Lançamento fascial. Terapia cognitivo-comportamental. O limiar de dor.

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Introduction

Fibromyalgia (FM) is documented as a common chronic musculoskeletal pain disorder and characterized by its symptom of chronic widespread pain with multiple tender points[1]. Tenderness, stiffness, mood disturbances (e.g. Depression and/or anxiety), and cognitive difficulties (e.g. Trouble concentrating, forgetfulness and disorganized thinking)[2–7]. In the general population the prevalence of FM ranges from 2–5% with more prevalence in female with ratio of 8-9:1-2 with male[8,9].

Cognitive-behavioral treatment programs have been developed to give patients with chronic pain the opportunity to reassess their beliefs about the relationship between pain and functioning and to experience that spontaneous safety behavior[10,11]. These treatment programs appear to be useful for managing the symptoms of FM[12,13], and these treatments have beneficial effects on pain and mood improvement.

Integrated physical therapy techniques are the combination of two or more therapeutic techniques used to treat any disorder. Massage-Myofascial release therapy improved pain, anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia[14]. Myofascial Release (MFR) applies the principles of biomechanical loading of soft tissue and the neural reflex modifications by stimulation of mechanoreceptors in the fascia (Greenman 1996; Lars Remvig et al 2008); It represents a widely employed manual technique specific for fascial tissues, to reduce adhesions, restore and/or optimise fascia sliding mobility in both acute and chronic conditions[15–17].

Deep transverse friction (DTF) massage is a technique used by James Cyriax and Gillean Russell to affect musculoskeletal structures of ligament, tendon and muscle to provide therapeutic movement over a small area (Prentice 2002). Hong et al. (1993) hypothesized that deep massage can offer effective stretching and mobilization of taut bands, and it's also reducing pain and tenderness of myofascial trigger point[18].

Many researchers have demonstrated the individual effects of these therapeutic techniques, still there are shortage of studies reporting synergism of physiotherapy and CBT as an indication in FM. Thus our aim of the study was to find out the combined effect of Cognitive Behavioral Therapy and Integrated Physiotherapy Techniques in Fibromyalgia and to evaluate the changes with the outcome measures to resolve the widespread musculoskeletal pain sensitivity and psychosocial scene and quality of life. Hence, we aimed to estimate the combined effect of cognitive behavioral therapy along with integrated physiotherapy techniques in the management of fibromyalgia symptoms. We hypothesize that there was no significance difference between cognitive behavioral therapy along with integrated physiotherapy and integrated physiotherapy alone on impact of fibromyalgia, pain, anxiety, depression, and quality of life (QOL) as null hypothesis and there was significant difference between cognitive behavioral therapy along with integrated physiotherapy and integrated physiotherapy alone as alternate hypothesis. Therefore, the objectives were to report the combined effect of cognitive behavioral therapy along with integrated physiotherapy techniques on the impact of fibromyalgia, pain, anxiety, depression, and QOL.

Methods

Recruitment of Participants

Patients with fibromyalgia (PwF) were recruited through two sources: (i) from the psychiatry department of Mahant Indiresh hospital and through flyers advertisement from various clinic associated with the college (Prayas healthcare centre, Outpatient department and Bala Pritham Hospital, Patel Nagar) at Dehradun, India. The inclusion criteria were as follows. Patients between the ages 18-50 years were eligible if they fulfill 2010 American College of Rheumatology (ACR) criteria like pain symptom must be present for at least 3 months and the widespread pain index (WPI) would be ≥ 7/19 and symptom severity (SS) score ≥ 5 or WPI 3-6 and SS scale ≥ 9;

and their pain level must be ≤ 4 on 10 point VAS scale. The following exclusion criteria were applied: any skin conditions and respiratory disorder affecting the implementation of protocol, spondylolisthesis / spinal canal stenosis, fractures for the past 1 year, any known recent surgery (< 1 year), any serious neurological injury (eg. Coma, Seizures), previous history of vascular disease, structural & functional leg length discrepancies, self reported or diagnosed Psychotic, or personality disorder. The study protocol was approved by the Institutional Review Boards, Punjabi University, Patiala. Written informed consent was obtained from all the patients. All procedures were in accordance with the ethical standards of the declaration of Helsinki, Revised 2013 and Good clinical practice. The study was conducted from March 2013 to June 2018. Eighty PwF were screened, 60 of whom were found eligible and recruited through purposive sampling for the two-group pretest-posttest randomized controlled study[19]. They were randomly assigned to one of the two groups with three month interventions: cognitive behavioral therapy (CBT) with integrated Physiotherapy or integrated physiotherapy (IPT) alone using block randomization using sequentially numbered opaque sealed envelope (SNOSE). There were four blocks in each rows with 15 rows, making the matrix design of 4 X 15. Each rows has two block for CBT with IPT and two for IPT alone. After one row has completed, another block of second row was opened and so on. Thus approximately equal number of patients in both the groups were maintained at any time and allocation bias were minimized.

The patient was managed for a period of 3 months. A 10 week session of cognitive behavioral therapy was administered along with the physiotherapy treatment on alternate days (Chart 1). The physiotherapy treatments included in the study are moist heat, ultrasound therapy, deep transverse friction and fascial release.

The CBT intervention mainly consists of two major components: cognitive restructuring, which focuses on reducing pain-specific dysfunctional cognitions (primarily PC), and coping, which focuses on teaching cognitive and behavioral coping strategies. Ten weekly 90-minute CBT group sessions (Thorn's Program 2004), including nine standard CBT sessions] and one specific session on PC (session 8). The duration of the intervention is 10 to 12 weeks. The program is structured as follows. Session 1: the connection between stress and pain. Session 2: identification of automated thoughts. Session 3: evaluation of automated thoughts. Session 4: questioning the automatic thoughts and constructing alternatives. Session 5: nuclear beliefs. Session 6: nuclear beliefs on pain. Session 7: changing coping mechanisms. Session 8: coping with ruminations, obsessions and worrying. Session 9: expressive writing. Session 10: assertive communication.

Session 8 is the additional PC session that begins after the coping session. This session is directed especially at participants who show high rumination. It consists of instructing the patients to write a story regarding the worst possible scenario for the future based on their greatest fear. This story should stress aspects that generate the greatest amount of malaise (for example, 'How do you see yourself in this situation?', 'What do you think?', 'How do you feel?', and so forth). The story is audiorecorded for a subsequent presentation to the patient. Patients are instructed to listen to this story for 30 to 60 minutes until it no longer causes anxiety. In general, this process takes between 10 and 15 sessions.

Chart 1. Thorn's Cognitive Behavioral Therapy Program

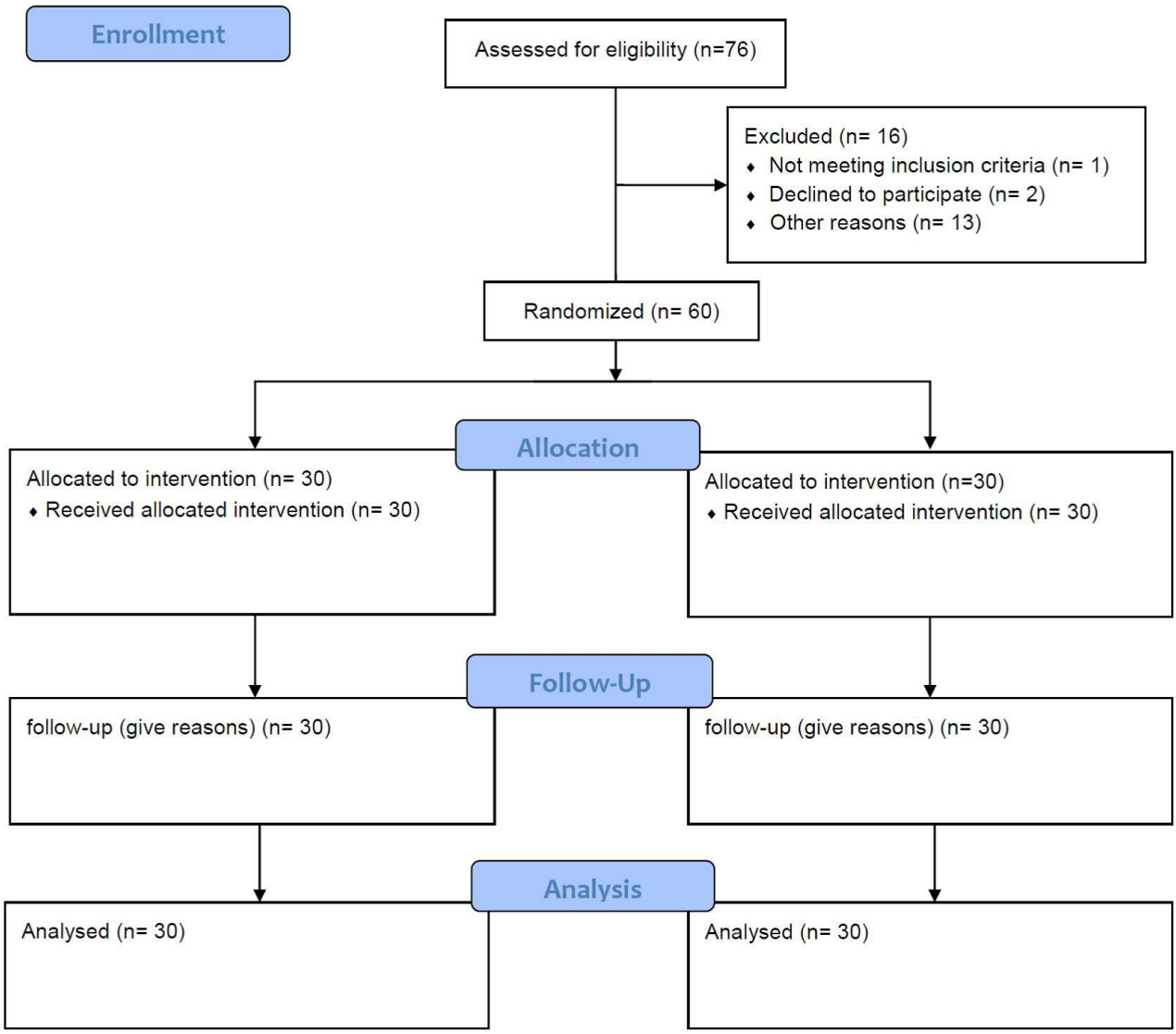
Session	Description
Week 1	Discussing the connection between chronic pain and FM
Week 2	Identification of automated thoughts.
Week 3	Evaluation of automated thoughts.
Week 4	Questioning the automatic thoughts and constructing alternatives.
Week 5	Nuclear beliefs.
Week 6	Nuclear beliefs on pain.
Week 7	Changing coping mechanisms.
Week 8	Coping with ruminations, obsessions and worrying.
Week 9	Expressive writing.
Week 10	Assertive communication.

The moist heat therapy was the first treatment mostly applied over the cervical, the low back area and the respective painful sites for 10 minutes. The Ultrasound (US) treatment was administered in a circular manner over the area of 2 x the size of the transducer (Ultrasound head) with a frequency of 3 MHZ in a continuous mode and a dose of 1.5 W/Cm2 was delivered at each tender point. The duration of the US treatment is 3 minutes of 3 session / week for 4 weeks.

Deep friction massage has been performed through the therapist fingers perpendicular to the exact site of lesion, with the depth of friction tolerable to the patient. The duration of the treatment was 5 minutes of 3 session / week for 12 weeks at each tender point.

Myofascial release (MFR) technique was applied using the cervical release, cranial base release, and leg pull over the point of restriction for at least 3 minutes. Enough rest time given in between the treatment repetitions to avoid any unnecessary fatigue. The CONSORT flowchart of the study is displayed in Figure 1.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow chart



Outcome measures

Revised fibromyalgia impact questionnaire (FIQR)[20] and SF 36 health survey for the quality of life (QOL)[21]. Also, Visual analogue scale (VAS) and Pressure algometric measurements were carried out for quantification of pain response. Measurement of pressure algometric readings were chosen based on the complaint of the participants, general anxiety disorder (GAD-7) scale[22] and beck depression index (BDI)[23] was recorded from the baseline (prior to treatment), first month, and second month and at the end of third month. Rater was blinded to the treatment.

Data analysis

The collected data were assessed for their normality using Kolmogorov–Smirnov test. As the data follow normal distribution, all the descriptive were expressed in mean ± standard deviation. Paired t test was incorporated to find out the statistical difference within Group- A and B in subjects with stress induced asthma. While independent t- test (students t - test) was utilized to compare the changes in mean values of all parameters between Group- A and Group- B. The data was analysed using statistical software, statistical package for social science (SPSS), IBM SPSS version 20.0 (Armonk, NY: IBM Corp.). The p-value ≤0.05 was considered to be statistically significant.

Result

The mean age of 30 patients recruited in CBT and IPT treatment group were 33.5 ± 8.3 years and 38.4 ± 9.4 respectively. Other demographic dimensions of patient with fibromyalgia recruited which includes gender, educational level, occupation, and marital status were displayed in Chart 2. The changes in the outcome measures, FIQR, BDI, VAS, GAD-7 and SF 36 health survey for the quality of life (QOL) and pain pressure threshold to different painful areas, were displayed in Chart 3-8 respectively.

Chart 2. Demographic dimensions which includes Gender, Educational level, Current Occupation, and Marital status of patient with fibromyalgia recruited

Demographic Dimensions		**Number of participants (Percentages)**	
		CBT	**IPT**
Age		**Mean ± SD**	**Mean ± SD**
		33.5 ± 8.3	38.4 ± 9.4
Demographic Characteristics		Number (Percentage)	Number (Percentage)
Gender	Male	11(36.7)	06 (20.0)
	Female	19(63.3)	24 (80.0)
Education level	No education	00	01 (3.3)
	Elementary	00	05 (16.7)
	Secondary	03 (10.0)	09 (30.0)
	Undergraduate	20 (66.7)	11 (36.7)
	Post-graduate	07 (13.3)	04 (13.3)
Current Occupation	No occupation	08 (26.7)	12 (40.0)
	Student	07 (13.3)	03 (10.0)
	School / Office assistant	03 (10.0)	07 (13.3)
	Business	05 (16.7)	03 (10.0)
	Professor / Teacher	05 (16.7)	01 (3.3)
	NCC / Police	02 (6.7)	01 (3.3)
	Bank Worker	00	01 (3.3)
	NGO	00	01 (3.3)
	Politician	00	01 (3.3)
	HR	00	00
Marital status	Married	23 (76.7)	22 (73.3)
	Unmarried	07 (13.3)	08 (26.7)
	Divorced	00	00

Chart 3. Changes in fibromyalgia impact questionnaire (FIQR) between cognitive behavioural therapy group and integrated physiotherapy group

Outcome variable	CBT group	IPT group	p-value
FIQR-Baseline	54.3 (41.3, 60.4)	60.2 (46.1, 73.9)	0.06
FIQR-4th week	37.6 (27.7, 47.1)	45.1 (32.9, 57.1)	0.02
FIQR-8th week	26.7 (21, 35.5)	33.8 (24.2, 39.8)	0.03
FIQR-12th week	21.6 (17.9, 24.9)	21.2 (17.9, 24.9)	0.85
Mean Difference Baseline – 12th week	32.7 (23.1, 42.7)	39.0 (30.2, 45.7)	0.04

Abbreviations: FIQR - fibromyalgia impact questionnaire

Chart 4. Changes in depression scores measured by beck depression index (BDI) between cognitive behavioural therapy group and integrated physiotherapy group

Outcome variable	CBT group	IPT group	p-value
BDI -Baseline	30 (19.5, 40.3)	22 (16.8, 26.3)	0.01
BDI -4th week	22.5 (15, 35.3)	20.5 (13.8, 25)	0.28
BDI -8th week	14 (9, 23.5)	15.5 (10.8, 25)	0.37
BDI -12th week	10.5 (6.8, 17.5)	13 (8.8, 18)	0.30
Mean Difference Baseline – 12th week	19.5 (12.4, 29.6)	9 (4.8, 14.2)	0.02

Abbreviations: BDI - beck depression index

Chart 5. Changes in pain scores measured by visual analogue scale (VAS) between cognitive behavioural therapy group and integrated physiotherapy group

Outcome variable	CBT group	IPT group	p-value
VAS -Baseline	8 (7.8, 10)	9 (8, 9)	0.96
VAS -4th week	5 (4, 6)	6 (4.8, 7)	0.14
VAS -8th week	3 (2, 4.3)	4 (2.8, 6)	0.02
VAS -12th week	2 (1, 3)	2 (1, 3)	0.75
Mean Difference Baseline – 12th week	6 (4, 7.9)	7 (4.9, 8)	0.34

Abbreviations: VAS - visual analogue scale

Chart 6. Changes in anxiety scores measured by general anxiety disorder (GAD-7) between cognitive behavioural therapy group and integrated physiotherapy group

Outcome variable	CBT group	IPT group	p-value
GAD-7 -Baseline	17 (12.8, 19)	15 (10.8, 17.3)	0.24
GAD-7 -4th week	13 (9.8, 15)	12 (10, 14)	0.38
GAD-7 -8th week	10 (6.8, 14.3)	10 (8, 14.3)	0.94
GAD-7 -12th week	9 (6, 11)	8.5 (3, 12)	0.51
Mean Difference Baseline – 12th week	8 (4.7, 12.3)	6.5 (4.2, 11.3)	0.26

Abbreviations: GAD-7 - general anxiety disorder

Chart 7. Changes in patient reported measured by 36-Item Short Form survey questionnaire – (SF-36) between cognitive behavioural therapy group and integrated physiotherapy group

Outcome variable	CBT group	IPT group	p-value
SF-36 PCS-Baseline	28.6 (14.4, 39.7)	31.5 (26.4, 37)	0.21
SF-36 PCS-4th week	40.7 (29.7, 65)	39.9 (32.8, 48.4)	0.79
SF-36 PCS-8th week	65 (49.6, 80.1)	47.5 (40.8, 55.2)	0.01
SF-36 PCS-12th week	73.7 (61.7, 87.7)	58.3 (49.5, 80)	0.03
Mean Difference PCS Baseline – 12th week	45.1 (34.2, 69.8)	26.8 (21.3, 34.7)	<0.001
SF-36 MCS-Baseline	30.7 (17.4, 45.2)	33.9 (28.4, 41.57)	0.37
SF-36 MCS-4th week	40.4 (31.8, 63.6)	38.5 (34.3, 43.2)	0.30
SF-36 MCS-8th week	65.7 (47.8, 78.1)	48.4 (42.3, 55.8)	0.01
SF-36 MCS-12th week	76.1 (59.4, 82.9)	51.8 (46.6, 74.3)	0.01
Mean Difference MCS Baseline – 12th week	45.4 (36.1, 69.2)	17.9 (12.1, 26.4)	<0.001

Abbreviations: PCS - Physical Component Summary; MCS - Mental Component summary; 36-Item Short Form survey questionnaire – SF-36

Chart 8. Changes in pain perception measured by pressure algometer between cognitive behavioural therapy group and integrated physiotherapy group

Outcome variable	Left			Right		
	CBT group	IPT group	p-value	CBT group	IPT group	p-value
SG-Baseline	1.15 (0.8, 1.6)	0.9 (0.7, 1.6)	0.41	1.1 (0.6, 1.8)	1 (0.7, 2)	0.52
SG-4th week	1.7 (1.1, 2.4)	1.4 (1, 2.1)	0.41	1.6 (1.2, 2.1)	1.3 (1.1, 2.3)	0.77
SG-8th week	2 (1.6, 2.8)	1.8 (1.3, 2.2)	0.17	2 (1.8, 2.6)	1.8 (1.4, 2.5)	0.35
SG-12th week	2.6 (2.2, 3.2)	2.2 (1.5, 2.8)	0.16	2.4 (2.2, 3.1)	2.4 (1.9, 2.8)	0.48
UA-Baseline	0 (0, 0)	0 (0, 1.4)	0.01	0 (0, 0)	0 (0.8, 1.6)	0.01
UA -4th week	0 (0, 0)	0 (0, 1.6)	0.01	0 (0, 0)	1.2 (0, 2.1)	0.01
UA -8th week	0 (0, 0)	0 (0, 2.1)	0.02	0 (0, 0)	1.2 (0, 2.4)	0.01
UA -12th week	0 (0, 0)	0 (0, 2.5)	0.01	0 (0, 0)	2 (0, 2.9)	0.01
LA-Baseline	0 (0, 0)	0 (0, 0)	0.89	0 (0, 0)	0 (0, 0)	0.94
LA -4th week	0 (0, 0)	0 (0, 0)	0.89	0 (0, 0)	0 (0, 0)	0.96
LA -8th week	0 (0, 0)	0 (0, 0)	0.89	0 (0, 0)	0 (0, 0)	0.98
LA -12th week	0 (0, 0)	0 (0, 0)	0.89	0 (0, 0)	0 (0, 0)	>0.99
HB-Baseline	1.7 (0, 2.1)	1.2 (0.4, 2)	0.44	1.5 (0, 2.2)	1 (0, 1.8)	0.47
HB-4th week	2 (0, 2.6)	1.5 (0.6, 2.3)	0.46	2 (0, 2.7)	1.4 (0, 2.2)	0.36
HB-8th week	2.4 (0, 3.1)	1.9 (0.9, 2.7)	0.43	2.4 (0, 2.9)	1.8 (0, 2.6)	0.41
HB-12th week	2.7 (0, 3.4)	2.4 (1.1, 3.2)	0.62	2.9 (0, 3.3)	2.4 (0, 2.9)	0.32

Abbreviations: SG – Shoulder Girdle; UA – Upper Arm; LA – Lower Arm; HB - Hip Buttock.

Discussion

Our finding found that the CBT combined with IPT treatment group shown significant result from baseline to third month. The reason why CBT combined with IPT have been beneficial to fibromyalgia patients because CBT have a therapeutic focus on coping strategies to appropriate environment, and increase in self-efficacy and sense of control, previous study also supports the results as CBT emphasizes modifying maladaptive thinking and behavioral responses to pain, and improve patients positive affect[24].

The CBT combined with IPT expanded self-appreciation dominance which assisted with relieving the negative thinking[25] and improved the positive thinking (self-question about their wellbeing and capacity to recover solid working, and self-expostulation) of the depressed mood patients[6,7,12].

In this study, the use of ultrasound improves sustained muscle contraction by increasing the permeability of the cell membrane; improves intracellular energy consumption; increases angiogenesis in ischemic tissues; and promotes tissue repair[26]. Also the Ultrasound combined with massage and exercise have an effect beyond placebo in myofascial pain syndrome treatment.

Pain pressure threshold: some of the trials that were evaluated in this review confirmed that Myofascial trigger point treatment is effective in reduce the pressure pain threshold, and visual analogue scale scores[27,28]. The reliability of the pressure pain threshold measurement using a pressure threshold meter (Algometer) has been studied in previous research[29,30]. Reeves et al. (1986) demonstrated the effectiveness of algometer as a reliable and valid measure of myofascial pain syndrome sensitivity.

MFR facilitate the release of fascial restrictions[31] and inhibit the gamma spindle response that causes the muscle to shorten when rapidly stretched. In favor to the result MFR shown a clinically important differences on the persistent plantar heel pain. Similarly, MFR was used to normalize the increased electrical activity of myofascial unit[23,24]; to decrease pain by its quality of sustained stretch and to restore the normal range of motion[17,20]. The pressure applied through transverse friction enables the production of fibroblasts and improve the recuperating and realignment of soft tissue[31]. PwF were recruited according to the ACR 2010 diagnostic criteria of fibromyalgia only and biomarker outcome measures not measured were the limitations of the study. Strengths were random allocation of the trial and by this allocation bias have been eliminated. Further the study could be extended as a multi-center trial using cluster randomization.

In nutshell, the CBT with IPT demonstrated more considerable improvement in the pain, pain pressure threshold, quality of life and physical and mental health than the integrated physiotherapy techniques. The combined effects of CBT and IPT modify maladaptive thinking and behavioral responses to pain, and typically either avoid patient's negative emotional experiences or attempts to reduce negative emotions as directly as possible[23], release fascial restrictions[35], facilitate the proliferation of fibroblasts, increases angiogenesis in ischemic tissues, and promotes tissue repair[36]. Thus, the results of the present study may help the clinicians to find a new way of combined use of integrated physiotherapy techniques along with cognitive behavioral therapy, to promote the patients with fibromyalgia in the future.

Conclusion

There is sufficient evidence to conclude that cognitive behavioral therapy combined with integrated physiotherapy treatment had significant positive effect to reduce the depression, disability, and improvement on the physical and mental health of patients with fibromyalgia.

Author contributions

Mozhi A participated in the search, collection of research data and statistical analysis of the research data, interpretation of results and writing of the scientific article. Arumugam N participated in the conception, design, analysis, statistics of research data and interpretation of results.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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