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A randomized controlled trial of mindfulness in patients with schizophrenia☆

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ABSTRACT

Cognitive Behavioral Therapy (CBT) is frequently used to attenuate the severity of positive schizophrenia symptoms; however, few studies have focused on attenuating negative symptoms. Recently, researchers have become interested in the effects of mindfulness-based intervention (MBI) on schizophrenia, but the lack of evidence-based results from random clinical trials (RCTs) has limited their effectiveness. Moreover, longitudinal data must be examined using appropriate study designs. We recruited 60 schizophrenia patients and randomly assigned them to an MBI or to a treatment-as-usual group. Negative symptoms, positive symptoms, mindfulness, and depression were assessed at baseline, post-course, and at a 3-month follow-up. Descriptive analysis and generalized estimating equations (GEEs) were used to examine the effects of MBI. We found that MBI mitigated the severity of negative symptoms and of general schizophrenic psychopathology except for the positive symptoms and for those of depression. Unexpectedly, we did not find long-term effect of mindfulness on negative symptoms. Larger sample sizes, long-term practical course, more rigorous study procedures, and a double-blind design should be considered in future studies.

1. Introduction

The lifetime prevalence of schizophrenia has been estimated to be 0.4% (Saha et al., 2005), and for decades schizophrenia has been considered and treated as a severe mental disease. Simeone et al. (2015) reported that the median prevalence of schizophrenia in 2014 was 0.33%, and that the worldwide lifetime prevalence was 0.49%. The overall prevalence in China ranged between 0.044% and 0.066% (Long et al., 2014). The prevalence of schizophrenia has been stable throughout the past few decades, and because the disease is extremely burdensome to schizophrenia patients and their caregivers (Hsiao and Tsai, 2014), efficacious treatments should be a biomedical priority. Better therapies would give patients and their caregivers more confidence about how to maintain a balanced and healthy lifestyle and, undoubtedly, more motivation to actually do it.

Cognitive Behavioral Therapy (CBT) is a strongly recommended management strategy for schizophrenia (Brus et al., 2012). CBT was originally developed to ameliorate depression and anxiety, and it was assumed that depression and its sequelae were maladaptive beliefs caused by disturbing life events (Roth et al., 2002). To treat schizophrenia, CBT was modified to focus on the beliefs about the symptoms and on how to cope with them by guiding the questions (Dickerson and Lehman, 2011). Evidence confirms that CBT has a strong attenuating effect on the severity of positive symptoms in patients with acute schizophrenia, but that it has only a small-to-moderate effect on the relapse of positive and negative symptoms (Hoffman et al., 2012). Effective schizophrenia intervention should focus on subjective well-being and quality of life, increased functional performance, and preventing relapses (Dickerson and Lehman, 2011).

More evidence that supports the beneficial effects of mindfulness-based intervention (MBI) on schizophrenia is accumulating (Khoury et al., 2013). Of five patients with severe schizophrenia who underwent eight MBI sessions and regular daily meditation for eight months, all reported significant mitigation in the severity of their hallucinations and delusions (Sheng et al., 2018). Moreover, a cross-sectional study (Dudley et al., 2018) reported that a higher extent of mindfulness attenuated distress when patients heard voices, and that self-compassion partially mediated between mindfulness on the severity of voices and distress. This indicates that mindfulness can be important for reducing the severity of symptoms and for increasing quality of life and subjective well-being.

MBI is a kind of psychological and behavioral practice based on Buddhist meditation, and it focuses on the awareness that emerges through purposely and nonjudgmentally paying attention in the present moment to the moment-by-moment unfolding of experience (Kabat-Zin, 2003). Practitioners of MBI for schizophrenia claim that its patients

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have reported relaxation, relief from psychological symptoms, cognitive change, and focus on the present (Brown et al., 2010). Schizophrenia patients developed emotions and beliefs that were more adaptive, and they said that MBI motivated them to more closely maintain balanced and healthy lifestyles (Tabak et al., 2015). However, many questions about the efficacy of MBI and the mechanism of mindfulness on schizophrenia await resolution (Chadwick, 2014).

Although confirmatory evidence of the benefits of MBI for schizophrenia patients is currently being reported by randomized clinical trials (RCTs), there are limits to its ability to attenuate schizophrenia symptoms, especially negative symptoms (Cramer et al., 2016). In Hong Kong, a larger-scale (n = 107) RCT on the effects of MBI on schizophrenia patients showed significantly ameliorated positive and negative symptoms after six months compared with patients who underwent only treatment-as-usual (TAU) (Chien and Thompson, 2014).

In the past, the paired t-test and analysis of variance (ANOVA) were frequently used to evaluate follow-up and longitudinal data. However, ANOVA and repeated measurements could not precisely present the changes of an individual to limit the effectiveness of intervention (Zeger et al., 1988). Generalized Estimating Equations (GEEs) can be used to analyze normal and non-normal data in RCTs and longitudinal studies (Bell et al., 2018). In the present study, we not only examined the effectiveness of mindfulness-based intervention on negative symptoms and psychotic symptoms, but also profiled the trend of changes in outcome measures on schizophrenia. Thus, we used GEEs to analyze our follow-up data.

In sum, the present study aimed to use randomly assigned and GEE analyses to examine the effect of MBI on the severity of psychotic symptoms in schizophrenia patients. We hypothesized that:

(1) At baseline, there would be no significant differences in the severities of positive symptoms, negative symptoms, general psychotic symptoms, and depression between the MBI and TAU groups.
(2) At baseline, there would be no significant differences in the extent of mindfulness between the MBI and TAU groups.
(3) Post-course, the severity of positive and negative symptoms in the MBI group would be significantly lower than in the TAU group.
(4) Post-course, the extent of mindfulness in the MBI group would be significantly higher than in the TAU group.
(5) At the 3-month follow-up, the severity of positive and negative symptoms in the MBI group would be significantly lower than in the TAU group.
(6) At the 3-month follow-up, the extent of mindfulness in the MBI group would be significantly higher than in the TAU group.

2. Methods

2.1. Study design

This RCT examined the effects of MBI on schizophrenia patients. PANSS scores at baseline, post-course, and follow-up between the MBI and TAU groups have been analyzed using repeated measures (Hsieh et al., 2018).

2.2. Patients and procedures

We recruited 60 schizophrenia patients from rehabilitation wards and daycare centers in mental hospitals in eastern Taiwan. All were referred by psychiatrists, nurses, occupational therapists, clinical psychologists, or volunteers. Yuli Hospital's Institutional Review Board approved the study protocol (YLH-IRB-10307). Inclusion criteria were (a) being 18–65 years old, (b) being diagnosed on the schizophrenia spectrum, (c) being able to read and write Taiwanese Mandarin Chinese, and (d) having at least an elementary school education. Patients with (a) psychotic symptoms, (b) delirium, or (c) extensive suicidal ideation, or (d) patients who were violent were excluded.

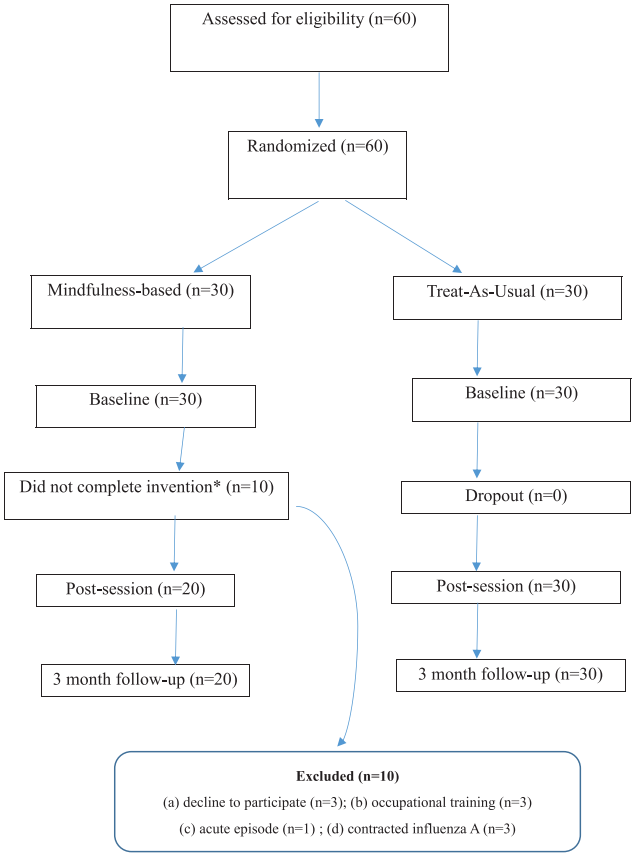

Fig. 1. CONSORT flowchart.
*: The participants who did not complete at least four sessions were treated as the participants who failed to intervention.

The research assistant stated the purpose of this project and explained each patient's personal rights and potential risks before they signed a written informed consent. Patients were then randomly assigned to the mindfulness group (MBI; n = 30) or to the treatment-as-usual group (TAU; n = 30). Before undergoing MBI, the baseline severity of the positive and negative symptoms, and the extent of the mindfulness, were all assessed. The research assistant was responsible for the interview and assisted participants on the completion of the self-report questionnaires. Two assessors were trained by experienced clinical psychologists. Before assessing, the principal researcher assessed the same participant with the assessors and discussed any inconsistent scores in order to improve the consensus. The same assessments were made after eight weeks of MBI and at the three-month follow-up. The CONSORT flowchart is shown in Fig. 1.

2.3. Interventions

2.3.1. Mindfulness-based interventions

We developed an eight-session, 1.5-h weekly MBI program for schizophrenia based on a self-awareness, self-regulation, and self-transcendence (S-ART) model of mindfulness (Vago and Silbersweig, 2012). S-ART assumes that mindfulness practice efficaciously regulates the behaviors, increases the awareness, and maintains a positive relationship between each patient's self and others. In the present study, the eight weeks of MBI primarily focused on practicing self-awareness and self-regulation. Three groups were led by six senior clinical psychologists who had undergone a 3-day MBI workshop and maintained daily mindfulness practice. During the 3-day workshop, trained therapists were taught the concepts of mindfulness, mindfully eating, mindfully walking, mindful yoga, mindful meditation, and

mindful self-compassion. After the workshop, they were asked to practice mindfulness daily throughout the week.

In the first week, patients were introduced to the concept of mindfulness and asked to meet the expectations of the MBI group. Homework was assigned at the end of each session. The second week, we invited the patients to play simple puzzle games to stimulate their curiosity. We then taught them a 15-min breathing mediation, which was assigned as daily homework. The third week, we invited the patients to mindfully write their name after their homework review. The fourth week, we taught them to mindfully eat and to allow themselves to experience the effect of habitual behaviors after their homework review. The fifth week, we asked the patients to mindfully read and write a short paper. In the sixth and seventh weeks, we asked them to mindfully stretch. The eighth week, we taught them self-compassionate meditation to increase their capacity for self-care and prosocial behavior. Each week, a 15-min breathing meditation was done before we gave the patients feedback and their homework assignment.

2.3.2. Treatment-as-Usual

All of our participants were recruited from rehabilitation wards and daycare centers. Before entering this study, all of the participants with residual symptoms were treated with routinely scheduled rehabilitations, such as, walking 5000 steps every morning, occupational rehabilitation twice a week, nutrition counseling, nursing care, health education group, mild doses of antipsychotic drugs, and other routine mental hospital activities. Thus, the participants in the TAU group were asked to maintain their routine activities.

2.4. Measurements

2.4.1. Personal information: included ID, gender, age, and length of formal education

2.4.1.1. Chinese version of the mindfulness attention awareness scale (MAAS). This scale was developed by Brown and Ryan (2003) to assess the extent of dispositional mindfulness. It is sensitive to improvements in the extent of a patient's mindfulness. Chang et al. (2011) translated the MAAS into Chinese and reported that it had good reliability and validity. It assesses fifteen items rated from 1 (Never) to 6 (Always). Higher scores mean a lower level of mindfulness.

2.4.1.2. Beck depression inventory (BDI-II). The scale was developed to assess the severity of depressive symptoms (Beck et al., 1988). There are 21 items rated from 0 to 4 that ask about different depression symptoms. Higher scores mean more severe depressive symptoms (Walter et al., 2003). Cronbach's α of the BDI-II after 8 sessions in this study was 0.90.

2.4.1.3. Scale for assessment of negative symptoms (SANS). The scale was developed by Andreasen (1982) to assess the severity of negative symptoms. Twenty-three items are rated from 0 (None) to 5 (Severe). Higher scores mean more severe negative symptoms. The reliabilities of the five subscales were: affective flattening (0.86), alogia (0.89), avolition (0.68), anhedonia (0.74), and attention impairment (0.86) (Andreasen et al., 2003).

2.4.1.4. Chinese Mandarin version of the positive and negative syndrome scale (CMV-PANSS). The PANSS includes 30 items rated from 1 to 7 that assess the severity of the positive and negative symptoms and of the general psychopathology of patients with schizophrenia. Higher scores mean more severe symptoms. The CMV-PANSS showed good reliability (Cronbach's α = 0.928) (Wu et al., 2015).

2.5. Statistical analysis

Intention to treat analysis (ITT) was used in the present study for two reasons (Gupta, 2011). First, ITT ignores noncompliance and withdrawal. Second, ITT preserved sample size in the present study. Our sample was small because it was difficult to recruit patients. Descriptive analyses, *t*-tests, and χ^2 tests were used to determine the distributions of demographic and outcome variables in the two groups. Generalized Estimating Equations (GEEs) are frequently recommended for analyzing longitudinal data when the data are not normally distributed and the variance of the outcome variables are not constant (Ghisletta and Spini, 2004). In the present study, GEEs were used to examine pre-course, post-course, and follow-up data. Significance was set at $p < 0.05$.

3. Results

3.1. Demographic data

Only 50 of the recruited patients completed the study: 3 dropped out because of occupational training, 3 contracted influenza A infection, 3 dropped out for personal reasons, and 1 had an acute psychotic episode before the intervention (see Fig. 1). The mean age of MBI group members was 54.43 ± 6.32 years and of TAU group members was 51.15 ± 6.32 years. There were no significant differences in the severity of SANS ($t = –1.649$, df = 56, $p = 0.105$), PANSS ($t = –0.788$, df = 55, $p = 0.434$), depressive symptoms ($t = 0.296$, df = 56, $p = 0.768$), or the level of mindfulness ($t = 0.566$, df = 56, $t = 0.574$) between dropouts and patients who completed the study, except for age ($t = –3.313$, df = 57, $p = 0.002$).

At baseline, there were no significant differences between the MBI and TAU groups in sex ($\chi2 = 1.482$, df = 1, $p = 0.223$) or educational level ($\chi2 = 6.663$, df = 4, $p = 0.155$), but TAU group members were significantly older than were the MBI group members ($t = 2.722$, df = 57, $p = 0.009$). There were no significant differences in outcome measures between the MBI and TAU groups in PANSS ($t = –0.388$, df = 55, $p = 0.699$), SANS ($t = –0.947$, df = 56, $p = 0.347$), level of mindfulness ($t = –1.793$, df = 56, $p = 0.078$), and depressive symptoms ($t = –0.610$, df = 56, $p = 0.545$) (Table 1).

3.2. GEE data

We treated age as a covariant because of the significant difference in age between the MBI and TAU groups.

3.2.1. The effects of mindfulness-based intervention on negative symptoms

GEE analysis showed a significant main effect of group on SANS (β = 0.661, $p = 0.011$) and a significant main effect of time on SANS at time 1 (β = 0.986, $p = 0.000$). The effect of group × time on SANS reached was significant after baseline (β = –0.973, $p = 0.000$) but not significant after the post-course (β = –0.1, $p = 0.53$).

The main effects of group (β = 0.996, $p = 0.000$) and at time 1 (β = 0.508, $p = 0.011$) were also significant for the changes of the negative symptoms subscale for PANSS. The effect of time × group after baseline was marginally significant (β = –0.439, $p = 0.049$) but not significant after the post-course (β = 0.18, $p = 0.44$) (see Fig. 2).

3.2.2. The effect of mindfulness-based intervention on psychotic symptoms

GEE analysis showed a significant main effect of group on the total scores of PANSS (β = 0.24, $p = 0.03$) and a significant main effect of time on the total scores of PANSS at time 1 (β = –0.223, $p = 0.000$). The effect of group × time on the total scores of PANSS was significant after baseline (β = –0.363, $p = 0.00$) but not significant after the post-course (β = –0.07, $p = 0.52$) (see Fig. 3).

The main effect of group on the changes in the general psychopathology subscale for PANSS was significant after baseline (β = –0.48, $p = 0.00$) but the main effect s of time (β = 0.22, $p = 0.049$) was marginally significant. The effect of time × group after baseline was also significant (β = –0.43, $p = 0.01$).

Table 1
Longitudinal outcome measures between TAU and MBI.

	MBI (N = 20) Mean	S.D	TAU(N = 30) Mean	S.D
SANS				
Baseline	1.95	0.74	1.64	0.48
Post-course	0.95	0.96	1.52	0.81
3-month follow up	0.89	0.20	0.94	0.17
PANSS				
Baseline	2.41	0.34	2.28	0.64
Post-course	2.68	0.39	2.98	0.43
3-month follow up	2.86	0.07	2.63	0.09
Mindfulness				
Baseline	1.69	0.24	1.54	0.31
Post-course	1.91	0.50	2.16	0.82
3-month follow up	3.97	1.12	3.98	1.43
Depression				
Baseline	0.46	0.20	0.42	0.26
Post-course	0.40	0.48	0.47	0.44
3-month follow up	0.42	0.48	0.27	0.26
Positive symptoms				
Baseline	2.13	0.41	1.96	0.62
Post-course	3.10	0.29	3.12	0.26
3-month follow up	3.14	0.23	3.10	0.08
Negative symptoms				
Baseline	3.09	0.80	3.13	1.64
Post-course	2.45	0.90	3.06	0.88
3-month follow up	2.10	0.63	2.58	0.81
General				
Baseline	2.35	0.35	2.15	0.60
Post-course	2.79	0.32	3.07	0.40
3-month follow up	2.82	0.31	3.08	0.50

SANS: Scale for Assessment Negative Symptoms; PANSS: Chinese Mandarin version Positive and Negative Syndrome Scale; Positive: the positive subscale of Chinese Mandarin version Positive and Negative Syndrome Scale; Negative: the negative subscale of Chinese Mandarin version Positive and Negative Syndrome Scale; General: the general psychopathology of Chinese Mandarin version Positive and Negative Syndrome Scale; Mindfulness: Chinese version of Mindfulness Attention Awareness Scale; Depression: Beck Depression Inventory II; *:$p < 0.05$; **:$p < 0.01$.

The main effect of group on the changes of the positive symptoms subscale for PANSS was not significant (β = –0.03, $p = 0.76$) but the main effect of time after baseline was significant (β = –1.01, $p = 0.00$). The effect of time × group after baseline was not significant after baseline (β = –0.14, $p = 0.40$) or after the post-course (β = 0.06, $p = 0.65$). (see Fig. 3)

3.2.3. The effects of mindfulness-based intervention on depression and the level of mindfulness

The main effects of group and time on depression were not significant at baseline (β = –0.15, $p = 0.20$; β = 0.04, $p = 0.76$). The effect of group × time on depression was significant after baseline and after the post-course (β = 0.12, $p = 0.39$; β = 0.22, $p = 0.07$) (See Fig. 4).

The main effect of group on mindfulness was not significant (β = 0.01, $p = 0.95$), but the main effect of time on mindfulness was significant (β = –0.30, $p = 0.01$). The effect of group × time on mindfulness was not a significant after baseline or after the post-course (β = –0.16, $p = 0.38$; β = 0.25, $p = 0.22$).

4. Discussion

4.1. Synthesis and interpretation of findings

We used an RCT design and GEEs to examine the effects of MBIs on the severity of the positive and negative symptoms of schizophrenia, on its depression, and on the extent of mindfulness in schizophrenia patients. After eight sessions mindfulness-based interventions, MBI group patients reported lower levels of SANS than did those in the TAU group, but at the 3-month follow-up there was no significant difference in SANS. The negative symptom subscale of PANSS in the MBI group was significantly lower at the 3-month follow-up than at baseline, but it was not in the TAU group. There was no significant difference in positive symptoms between the groups post-course or at the 3-month follow-up. The level of general psychopathology of MBI group patients rose more slowly from baseline to the 3-month follow-up than in the TAU group.

First, we found that, after the interventions, the SANS of the MBI group patients was better (lower) than that of the Tau group patients. Despite a slight rise during the follow-up, the severity of the MBI group's negative symptoms continued to be significantly lower. This was consistent with Johnson et al. (2009), a qualitative study in which patients used breathing and loving-kindness meditation to reduce the severity of negative symptoms. Patients had positive emotions and felt closer to family and friends during these two MBIs; they were peaceful and more concentrated on the here-and-now when they practiced breathing meditation. Therefore, the severities of anhedonia and attention impairment were attenuated.

Second, in addition to SANS, the negative symptom subscale levels of PANSS significantly decreased over time in the MBI group at post-course and during the follow-up. Our findings were consistent with those of Chien and Lee (2013). Moreover, our findings preliminarily supported the efficacy of MBIs for improving the negative symptoms of schizophrenia. Schizophrenia patients are encouraged to actively be aware of and to experience life through mindfully eating and mindfully stretching. Therefore, they have to refocus on their everyday activities and reengage with them to be aware of and to share them. The negative symptoms of avolition and affective flattening were attenuated after these MBIs. Future studies might want to examine the unique effects of each MBI on schizophrenia.

Third, we were unable to confirm the effect of mindfulness on the positive symptom scale of PANSS in the present study. Our data were

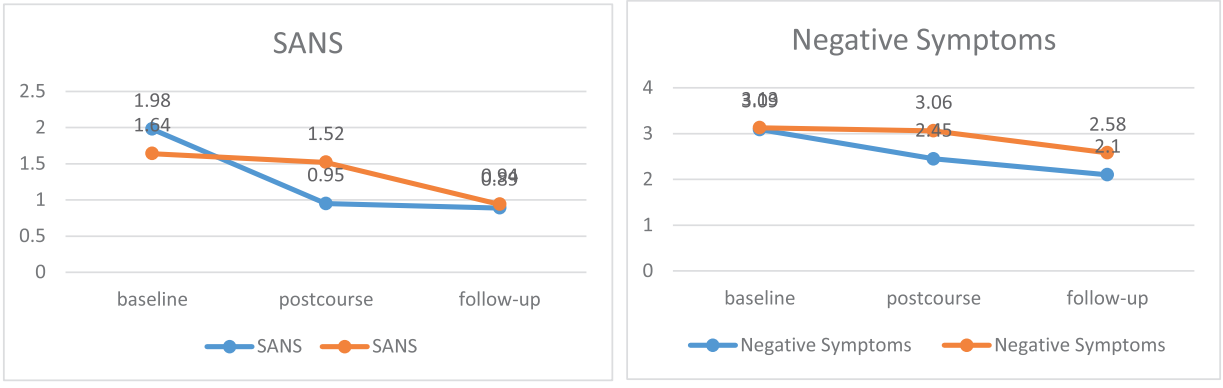

Fig. 2. Changes of negative symptoms between MBI and TAU.

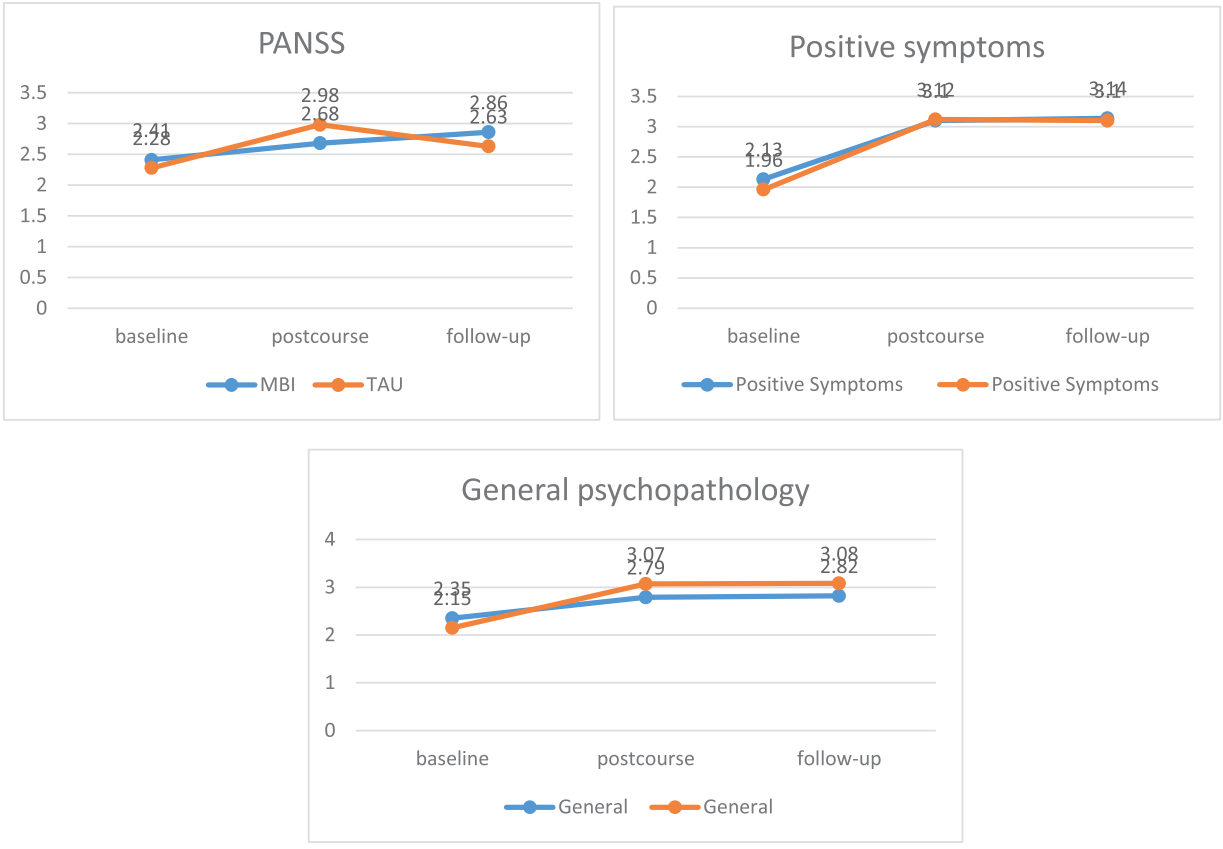

Fig. 3. Changes of positive symptoms and general psychopathology between MBI and TAU.

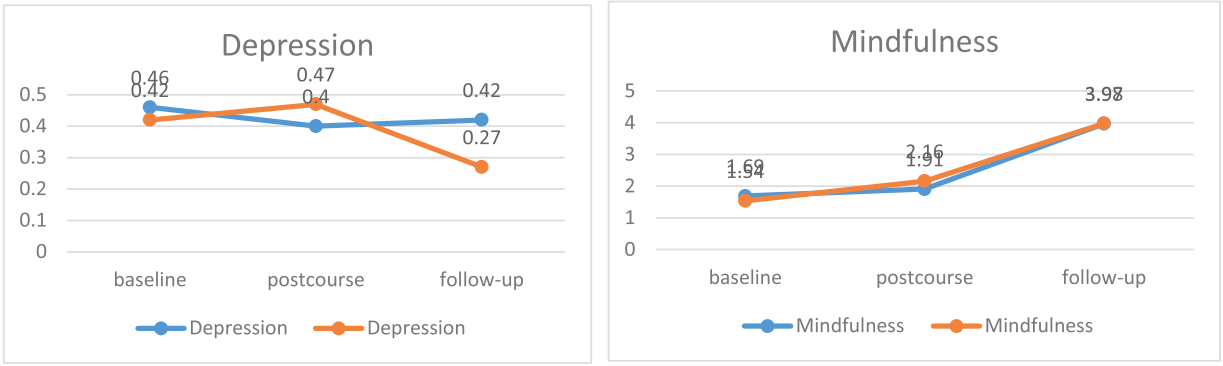

Fig. 4. Changes of depression and mindfulness between MBI and TAU.

inconsistent with those of Chien and Lee (2013). However, few studies have examined the effects of MBIs on positive symptoms by directly assessing PANSS or by measuring positive symptoms. For example, Chadwick et al. (2005) used the Clinical Outcomes in Routine Evaluation Outcome Measure (CORE-OM) to assess the changes of positive symptoms after MBI, and they reported that overall psychotic symptoms were mitigated by breathing meditation. In the present study, the effects of group and of time on negative symptoms were significant. The effect of time by group was not significant, possibly because the severity of negative symptoms is not stable and gradually improves even without interventions. A meta-analysis (Savill et al., 2015) claimed that the severity of negative symptoms decreased across all conditions, but more longitudinal studies are required to confirm this.

Fourth, we found that general levels of the psychopathology of schizophrenia had been mitigated after MBI, which is consistent with Chien and Thompson (2014). The schizophrenia patients in the present study were asked to read mindfully and to do breathing and loving-kindness meditation for others and for themselves. These practices not only helped patients learn to calm down, but also taught them to become aware of and able to regulate their emotions. Theoretically, schizophrenia patients who accept MBIs can regulate the pathways of their brain circuits, especially for amygdala and other emotional-load pathways (Dickerson and Lehman, 2011; Dudley et al., 2018). The biomarker of mindfulness should be identified in future studies.

Fifth, we found in our study no significant difference in the extent of mindfulness between the MBI and TAU groups. Despite our finding of a marginal effect of time by group, this is inconsistent with Chien and Thompson (2014). One possible explanation is that the MBI in the present study was short-term. It was also shorter than that of Sheng et al. (2018), who claimed that long-term practice to cultivate mindfulness is necessary. Further study should increase the times of mindfulness-based course for schizophrenia in order to deeply cultivate the level of mindfulness.

Sixth, we found no significant differences in depression severity

over time or between subjects, which did not support Brown et al. (2010). One possible explanation is the severity of depressive symptoms. In the present study, the average levels of depression at baseline, post-course, and during the 3-month follow-up were 9.27, 8.98, and 7.16, respectively. Thus, the BDI-II means mentioned above were at normal depression levels. Therefore, future studies might consider inviting participants with more severe depressive symptoms in order to examine the effects of MBIs on depression in schizophrenia.

4.2. Limitations

Our study has some limitations. First, because our sample was small, our findings cannot be generalized to other populations. A large sample should be used in future studies. Second, the doses of prescribed medications and relevant information about symptom or disease onset could not be collected in this study. Third, despite being asked to objectively measure the severity of negative symptoms or general psychopathology, the assessors were not blinded to the treatment and control groups. A double-blind study should be conducted in the future. Finally, although practicing MBIs at home was assigned after each session, we did not assess patient adherence. According to therapists' feedback, the participants in the MBI group reported that they had completed their home practice after each session. Patient adherence should be assessed in future studies. Although our study was an RCT, our findings did not fully support the efficacy of MBI because we did not compare it with another type of active intervention. Future studies should compare MBI with other types of schizophrenia interventions.

5. Conclusions

Our findings preliminarily support the efficacy of MBI for schizophrenia. Additional studies are needed to explain the mechanism of mindfulness and to confirm its efficacy for schizophrenia.

Compliance with ethical standards

Funding: This study was funded by Yuli Hospital, Taiwan Ministry of Health and Welfare (grant number: YHL-IRP-10404).

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.02.079.

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