A randomised controlled trial of comprehensive early intervention care in patients with first-episode psychosis in Japan: 1.5-year outcomes from the J-CAP study

ABSTRACT

Background: The first episode of psychosis represents a critical period wherein comprehensive early intervention may alter the course of illness. However, evidence from randomized controlled trials which examined the impact of comprehensive early intervention care is limited.

Aims: To conduct a multi-centre trial comparing comprehensive early intervention care and standard care in young patients with first-episode psychosis (FEP) in Japan.

Method: Individuals with FEP (ages 15–35 years) were randomised to receive standard care or specialized comprehensive care and were followed-up until 1.5 years (trial no.: UMIN000005092).

Results: The specialized care group had a lower treatment dropout rate (odds ratio, 0.038; 95% confidence interval, 0.002–0.923) and higher clinical remission rate (odds ratio, 6.3; 95% confidence interval, 1.0–37.9) than the standard care group, even after adjusting for baseline characteristics.

Conclusions: Comprehensive early intervention care may provide advantages over standard care in Japanese patients with FEP.

Declaration of Interest: None.

INTRODUCTION

In recent decades, several early intervention services have been established to target young individuals with first-episode psychosis (FEP). Early intervention is based on the hypothesis that the initial years of psychosis represent a critical period in which comprehensive early intervention care can alter the course of the illness. Yet, few randomised controlled trials have assessed the effects of comprehensive early intervention care programs in individuals with FEP. The results of previous randomised studies conducted in Denmark (OPUS trial[1-3]), England (LEO trial[4, 5]) and the United States (STEP trials[6] and the RAISE trial[7, 8]) suggest that specialized comprehensive care for FEP promotes clinical and functional recovery assessed after 1–2 years of therapy. Only one randomised controlled trial examined the effect of a 1-year extension for specialized early intervention care in an Asian population of patients with FEP,[9, 10] and no study to date has compared specialized early care and standard care in a young Asian population of patients with FEP. Accordingly, we investigated whether comprehensive early intervention care produces better outcomes than standard care in young individuals with FEP in Japan using a multi-centre randomised controlled design. We hypothesized that comprehensive early intervention care would increase the likelihood of clinical and functional recovery and decrease the treatment dropout rate at 1.5-year follow-up.

METHOD

This study was conducted as a part of the Japanese Comprehensive Approach for First-episode

Psychosis (J-CAP) study. The aim of the J-CAP study was to develop, test, and implement comprehensive early intervention care approaches for young people with FEP. The background, rationale, and design of the J-CAP study have been previously described elsewhere.[11]

Subjects

A total of 77 individuals were enrolled in the study (CONSORT diagram shown in **Figure 1**). Candidate participants were patients who received a diagnosis of F2 or F3 with psychotic symptoms as per the International Classification of Disease, 10th revision at a participating clinical site. The inclusion criteria were: (1) first-episode psychosis; (2) age between 15–35 years; (3) onset of franc psychotic symptoms in the previous 5 years; and (4) residence in the catchment area of each clinical site. The onset of psychotic symptom was defined as the first clear evidence of a psychotic symptom (i.e., delusion, hallucination, or thought disorder) scored 4 or higher on the Positive and Negative Symptom Scales (PANSS[12]). The exclusion criteria were: (1) a premorbid intelligence quotient of < 80; (2) inability to sufficiently communicate in Japanese; (3) requirement of care for any organic mental disorder or inpatient care for any physical condition; (4) history of dependency on alcohol and/or other substances; (5) completion of electroconvulsive therapy and/or transcranial magnetic stimulation therapy within the past month; and (5) any patient deemed ineligible by the attending physician for any other reason. Although the use of substances such as cannabis has become a major issue worldwide, a very small number of young people use these drugs in Japan.[13] Therefore, we adopted a history of continuous substance

dependence as an exclusion criterion in this trial. All patients were assessed for eligibility by psychiatrists at each participating site.

Written informed consent was obtained from all participants and from the legal guardians of participants younger than 20 years of age. The study was approved by the institutional review boards of the coordinating centre and participating sites (Tokyo Metropolitan Institute of Psychiatry, no. H22-23; University of Tokyo, no. 3307; Matsuzawa, no. 22-23; Mie, no. H23.2.21; Okayama, no. H24-6; and Hinaga, no. H22.12.22). The J-CAP Safety Monitoring Board provided study oversight.

Clinical sites and randomisation

The study was conducted at 5 clinical mental health sites in 3 cities: The University of Tokyo Hospital, Tokyo Metropolitan Matsuzawa Hospital, Mie Prefectural Mental Medical Center, Hinaga General Center for Mental Care and Sasagawa Clinic, and Okayama Mental Medical Centre. Relevant details for these sites are summarised in **Table S1**. The site eligibility criteria were having an early intervention service for people with FEP and more than 2 clinicians who participated in the early intervention training program provided by clinical experts on early intervention for psychosis in England (Dr. Jo Smith and Dr. Paul French).

The J-CAP was designed as an interventional, parallel, single-blinded (open label but blinded raters) trial. Participants were randomly assigned to the specialized comprehensive early intervention care approach (CAP) group or to a standard care (SC) group. In the CAP group, an

early intervention team provided comprehensive community-based care for 18 months. In the SC group, participants received standard care for 18 months.

Assessments of clinical and functional data were conducted upon enrolment and at the 18-month follow-up. While the target sample size was originally 150,[11] we were unable to recruit a sufficient number of participants even after the registration period was extended by the study committee. The study committee stopped recruitment on September 30, 2014 when we achieved a sample size sufficient to evaluate an important secondary outcome (i.e., dropout from treatment).[14] This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) and accepted by the International Committee of Medical Journal Editors (ICMJE) (no. UMIN000005092).

Interventions

Comprehensive early intervention community-based care was provided over a period of 18 months after study enrolment by specialized CAP teams consisting of trained case managers and psychiatrists. CAP teams followed the clinical guideline and practice manual for promoting recovery from early psychosis[15, 16] and tailored interventions with established efficacy to meet the needs of young patients and their families. Case managers sought to promote patient clinical and functional recovery using a combination of cognitive-behavioural psychotherapy, family education and support, support for vocational and educational recovery, and relapse prevention strategies. Psychiatrists in the CAP group discussed about pharmacological therapy with case

managers and prescribed medicines in accordance with the clinical manual for FEP.[15, 16] The care components of the CAP have been previously described elsewhere[11]. To standardize the intensity and quality of comprehensive early intervention care, CAP teams participated in follow-up training courses and supervision meetings at least twice per year. Supervisors in the CAP coordinating centre (Tokyo Metropolitan Institute of Medical Sciences) who provided supervision for the CAP teams at each clinical site were trained and supervised by clinical experts on early intervention for psychosis in England (Dr. Jo Smith and Dr. Paul French).

Standard care (SC) or "community care as usual" included psychosis treatment as prescribed by a clinician choice and service availability. Clinicians who provided standard care received no additional training or supervision except for guidance regarding subject recruitment.

Assessments

We adopted the function domain score of the global assessment of functioning (GAF-F)[17] as a primary outcome measure. Other outcome measures were dropout rate, remission rate based on Positive and Negative Syndrome Scale (PANSS) scores,[18] PANSS total score, World Health Organization Quality of Life 26-item version (WHO-QOL 26[19, 20]) score, educational and vocational recovery rates, and care satisfaction of participants and families. The GAF-F, dropout rate, remission rate, and PANSS were evaluated by blinded raters and other measurements were assessed by self-report questionnaire.

GAF-F

The Global Assessment of Functioning (GAF[21]) records the current objective symptomatic and functional statuses of participants on an analogue scale ranging from 0 (poor) to 100 (good). We used the modified GAF scale[17] to assess functional and symptomatic statuses separately and to calculate GAF-F and GAF-S scores. The GAF-F rates social and occupational function and the GAF-S rates symptoms. The Japanese version of the modified GAF has been previously validated[22].

Dropout rate

Dropout rate was defined on follow-up point as the refusal of further treatment despite a need for treatment and several attempts at reengagement (phone calls to patients in both groups and home visits to participants in the CAP group).

Remission rate

Remission rate was defined using a proposal from the Remission in Schizophrenia Working Group[18] that defined symptomatic remission of illness as mild or less on all items of 8 PANSS subscores (P1, P2, P3, N1, N4, N6, G5, and G9), maintained for at least 6 months.

PANSS

The PANSS evaluates the current objective symptoms of patients using 30 items in 3 domains:

positive symptoms, negative symptoms, and general psychopathology.[12] Each item is rated from 1 (absent) to 7 (extreme), and the total score ranges from 30 to 210.

WHO-QOL 26

The WHO-QOL 26 assesses the current subjective satisfaction of participants with their quality of life using 26 items in 4 domains: physical health, psychological health, social relationships, and environment.[19,20] Each item is rated from 1 (poor) to 5 (good), and the total score is calculated as the average of all subscores.

Occupational/educational recovery rate

Occupational/educational recovery was assessed using the definition sheet from the UK National EDEN study[23]. We used the "training and occupation" section, which is rated from 0 (employment) to 4 (not in education, employment or training), to assess participant's recovery status. We rated scores based on each participant's best occupational/educational status achieved within the last 6 months at baseline and follow-up.

Care satisfaction

Care satisfaction was evaluated using a single item rated from 1 (very satisfied) to 4 (very dissatisfied). Participants and their families provided subjective care satisfaction ratings after study participation.

Statistical analysis

We analysed the data on an intention-to-treat basis. To examine effects of the intervention, we used t-tests to compare mean differences and confidence intervals for continuous variables between groups. Multilevel linear and multilevel logistic regressions were used to examine effects of the intervention while adjusting for baseline characteristics. Because data were taken from multiple patients from each clinical site, multilevel modelling was used for multivariate analyses. The model included random effect for each clinical site to account for within-site correlations. All statistical analyses were conducted using Stata MP for Windows, version 14.0 (StataCorp, College Station, Texas, USA). The two-tailed significance level was set at 0.05.

Results

Baseline characteristics of the study participants are shown in **Table 1.** A total of 77 participants were enrolled; of these, 40 were randomised to the CAP group and 37 to the SC group. Participants were predominantly living with their families (87%) and 51% were male. The mean age at baseline was 23.0 years (standard deviation = 5.1 years) and the mean duration of untreated psychosis was 16.8 months (standard deviation = 14.1 months; median = 12.7 months). Seventy-five participants were diagnosed as F2 and 2 participants were diagnosed as F3. There were no significant between-group differences in baseline clinical or functional characteristics except for symptom severity (PANSS total score: $P = 0.003$).

GAF-F scores in the CAP group at the 18-month follow-up were slightly higher than those in the SC group, but this difference was not statistically significant before (P = 0.195) or after adjusting for baseline variables (P = 0.332) (**Table 2**); however, the CAP group had a significantly lower dropout rate (2.5% vs. 21.6%; odds ratio [OR] = 0.038, 95% confidence interval [CI] = 0.002–0.923, P = 0.045) and significantly higher remission rate (OR = 6.29, 95% CI = 1.04, 95%on P = 0.045) than the SC group, even after adjusting for baseline variables. Family member care satisfaction was also significantly higher in the CAP group than in the SC group (OR = 3.69, 95% CI = 1.05–13.00, P = 0.042), but this difference did not remain significant after adjusting for baseline characteristics (P = 0.697). No significant group differences were found for symptom severity, medication dose, quality of life, recovery rate, or participant care satisfaction.

Discussion

In the present study, we found that young patients with FEP who received specialized comprehensive early intervention care had a decreased risk of dropout and increased clinical remission, as compared with those who received standard care; however, we did not identify significant between-group differences in functional outcomes. Dropout from mental health services is an important issue for young people with FEP,[24] especially given that outcome trajectories are established relatively early, usually during the first 2–5 years after illness onset.[25] A recent meta-analysis reported that specialized early intervention care for individuals with FEP

reduced the risk of dropout from treatment,[26] although dropout rates remain high (20.5–40%) even in the context of these specialized programs.[24] Compared with these previous studies, the dropout rate in our CAP group was quite low (2.5%); this may have been due to our sampling criteria, as we excluded individuals with comorbid substance use disorders, which have been identified as risk factors for service disengagement in other countries.[24] Statistically robust improvements in the clinical remission rate in our CAP group are consistent with the findings of a previous study where specialized care was provided for early psychosis.[27] Current multicomponent treatment programs for FEP emphasize a combination of psychosocial and pharmacological interventions as the first line treatment,[28, 29] and evidence suggests that this combined treatment approach promotes clinical remission among individuals with FEP compared to medication alone.[30, 31] To this end, we noted that lower doses of antipsychotics were prescribed to patients in our CAP group compared to the SC group. International treatment guidelines for FEP recommend the use of low-dose antipsychotic medication,[15] as high or excessive medication can increase the risk of physical health deterioration and poor functional recovery in young patients with FEP.[32] Taken together, these findings suggest that comprehensive early intervention care can reduce the risk of high or excessive antipsychotic medication use and associated adverse outcomes.

To the best of our knowledge, this is the first randomised controlled trial to examine effects of comprehensive early intervention care in an Asian cohort of young individuals with FEP. While we provide evidence that comprehensive early intervention care reduces treatment dropout

and promotes clinical remission, several important study limitations should be considered. First, our sample size was not large enough to detect changes in the primary outcome measure. As a result, the statistical power of our trial was limited. Second, the follow-up duration in our study was shorter than those in similar previous studies.[3, 5] The OPUS trial in Denmark reported that the benefits of specialized early intervention care in patients with FEP were most notable after 2 and 5 years of treatment, whereas positive effects were diminished at 10-year follow-up,[3] and a similar pattern was seen in the LEO trial in the UK that used a 5-year follow-up period.[5] Accordingly, a longer follow-up period may be required to investigate the sustainable efficiency of CAP treatment in future studies. Third, there were no physical health outcomes in our J-CAP study. Psychotic disorders are associated with a 10–30-year gap in life expectancy relative to the general population[33, 34] and premature mortality has been related to higher incidences of cardiovascular disease and obesity-related cancers in these patients.[35] Recent studies have shown a high prevalence of cardiometabolic risk factors among young people with first-episode schizophrenia spectrum disorders.[36] Future studies should include physical health-related outcomes as important targets of early intervention programs for young people with FEP.[37]

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Declaration of Interest

None.

Authorship

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