Ifenprodil tartrate treatment of adolescents with post-traumatic stress disorder: A double-blind, placebo-controlled trial

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\textbf{ABSTRACT}

\textbf{Background:} Several lines of evidence suggest that glutamatergic neurotransmission via the N-methyl-D-aspartate (NMDA) receptor plays a role in certain behavioral manifestations common to Post-Traumatic Stress Disorder (PTSD). Ifenprodil tartrate is a neuroprotective agent that binds to the GluN2B subunit of the NMDA receptor. The aim of this study is to confirm whether ifenprodil tartrate is effective in the adolescent PTSD patients.

\textbf{Methods:} This is a randomized, double-blind, placebo-controlled trial. Ten adolescent (13 to 18 years old) PTSD patients were randomized into two arms: placebo (n = 4), 40 mg/day ifenprodil tartrate (n = 6) for 4 weeks. All of the patients were assessed by IES-R-J (Primary outcome measure), TSCC-J, CDRS-R, DSRS-C-J and CGI-I.

\textbf{Results:} A comparison of baseline IES-R-J total scores and 4-week end-point scores showed a mild trend of improvement (p = 0.0895) and the difference score was -9.314. A comparison of baseline scores and 2-week intermediate-point scores showed that IES-R-J hyperarousal subscores and TSCC-J subscores (dissociation subscores, sexual concerns subscores) improved significantly. A comparison of baseline TSCC-J sexual concerns subscores and 4-week end-point scores improved significantly.

\textbf{Conclusions:} Our study may prove to be a short-term effective alternative safe treatment for adolescent patients with PTSD.

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1. Introduction

Post-traumatic stress disorder (PTSD) is a painful condition that has been recognized as a pathological response to severe psychological trauma (American Psychiatric Association, 1994, 2013). A meta-analysis showed that approx. 16% (95\%CI: 11.5–21.5) of trauma-exposed youth developed PTSD (Hoskins et al., 2015). However, the precise mechanisms of PTSD are currently unknown, and there are currently no standard pharmacological interventions for preventing child and adolescent PTSD (Amos et al., 2014). A systematic review (Sin et al., 2017) of psychological interventions for PTSD showed that the results from trials of trauma-focused cognitive behavioral therapy (TF-CBT) are limited and inconclusive regarding the effectiveness of this therapy on PTSD symptoms. Only one trial evaluated eye movement desensitization and reprocessing (EMDR) and provided limited favorable preliminary evidence compared to be on a waiting list for PTSD treatment. These findings are mostly based on low- to very low-quality evidence for PTSD (Sin et al., 2017).

Several lines of evidence suggest that glutamatergic neurotransmission via the N-methyl-D-aspartate (NMDA) receptor plays a role in certain behavioral manifestations common to PTSD, including dissociation and perceptual alterations (Chambers et al., 1999). Ifenprodil tartrate (brand name Cerocral\textsuperscript{®}), a neuroprotective agent that binds to the GluN2B subunit of the NMDA receptor (Williams, 2001), is used as a...
cerebral vasodilator in a limited number of countries including Japan and France.

Ifenprodil is a prototypical antagonist of the GluN2B subunit on the NMDA receptor (Hashimoto et al., 2013). Ifenprodil binds to the α1 adrenergic and NMDA receptors, and we reported that ifenprodil is also a potent agonist at the sigma-1 receptor chaperone on the endoplasmic reticulum (ER) (Ishima and Hashimoto, 2012). Sigma-1 receptor agonists can stimulate chaperone activity on the ER, thus enabling the regulation of neuronal plasticity in the brain, suggesting a potential role of sigma-1 receptors in the pathophysiology of a number of neuropsychiatric disorders (Hayashi and Su, 2007). In addition, ifenprodil is also an inhibitor of G protein-activated inwardly rectifying K+ (GIRK) channels, which play an important role in reducing neuronal excitability in most brain regions (Hashimoto et al., 2013). The NMDA receptors are crucial for the synaptic plasticity underlying learning and memory, and glutamatergic neurotransmission via NMDA receptors plays a role in the pathophysiology of PTSD (Hashimoto et al., 2013, Wolosker and Balu, 2020). Both systemic and intra-amygdala treatments with ifenprodil before extinction training impaired the initial acquisition and subsequent retrieval of fear extinction (Myers et al., 2011). These findings suggested that the acquisition of fear extinction requires the activation of GluN2B subunit on the NMDA receptors, and that the lateral amygdala is an essential brain region underlying its mechanism (Hashimoto et al., 2013). In addition, accumulating evidence has emerged about the effectiveness of the α1 adrenergic receptor antagonist prazosin in the treatment of nightmares and hyperarousal among patients with PTSD treated within the U.S. Department of Veterans Affairs (Harpaz-Rotem and Rosenheck, 2009), suggesting the role of α1 adrenergic receptor in the treatment of PTSD. Taking the past and present findings together, we speculate that with the high affinity for the NMDA receptors, α1 adrenergic receptors, sigma-1 receptors, and GIRQ channels, it is likely that ifenprodil acts at least partially on these targets in PTSD patients. Furthermore, we reported that ifenprodil tartrate was effective in the treatment of flashbacks in three female adolescent PTSD patients with a history of childhood sexual abuse (Kishimoto et al., 2012), and it was also effective in the treatment of flashbacks in three female adolescent PTSD patients with a history of childhood abuse (Sasaki et al., 2013). We conducted the present study to determine whether ifenprodil tartrate is effective in the treatment of adolescents with PTSD.

2. Methods

2.1. Ethics statement

This study was performed in accord with the Declaration of Helsinki II. The Institutional Review Board of Chiba University Hospital approved the study protocol (approval no. G25013). After receiving a full explanation of the study as well as any potential risks and benefits, all subjects (person him/herself and legally acceptable representative) provided written informed consent for participation in the study.

2.2. Study design and subjects

This was a randomized, double-blind, placebo controlled, parallel group study performed at Chiba university Hospital. The study protocol has been described (Sasaki et al., 2017). Adolescents (13–18 years old) with PTSD (Chiba University Hospital outpatients) were randomized into two arms: placebo or 40 mg/day ifenprodil tartrate for 4 weeks. All of the subjects were diagnosed as having PTSD based on the DSM-IV criteria (American Psychiatric Association, 1994). The inclusion and exclusion criteria are listed in Table 1. We had originally planned to have 40 subjects at Chiba University Hospital.

2.3. Randomisation and masking

At the Clinical Research Data Center in Chiba University Hospital, the information required for case registration was entered into the data system and cases were randomly assigned to the placebo and true medication groups by computer application in the Data Center. Randomization was undertaken by a computer-based minimization algorithm stratified by sex and IES-R-J scores (Asukai et al., 2002) (♂=45, <45). The allocated group number, according to the sequence, was then sealed in opaque envelopes and received by the participant medication distributor in order of entry to the study. The list of randomized patients was kept at the data center until the study data were fixed. We used the Cerocal fine granule 4%/20 mg ifenprodil tartrate/0.5 g [ifenprodil tartrate and excipient]; Sanofi K.K. (Tokyo, Japan), Nichi-iko Pharmaceutical Co., Ltd (Toyama, Japan). The placebo was composed of lactate only. Cerocal fine granule is ground down to be similar to fine lactate. Ifenprodil tartrate and placebo (powder) were completely identical in terms of size, shape, color, and smell, and the subjects and outcome assessors were not able to differentiate them (Fig. 1). Moreover, the subjects, outcome assessors, research coordinators, and medication distributors were all blinded to the allocations. These methods are partly similar to our previous study (Kotajima-Murakami et al., 2019).

2.4. Procedures: intervention

The placebo in the placebo group consisted of the fine lactate only,
taken orally as 1 g per pack; one pack after breakfast and one pack after supper. The drug in the 20 mg/pack ifenprodil group was 0.5 g of fine lactate and 0.5 g of Cerocral fine granule taken orally as 1 g per pack; one pack after breakfast and one pack after supper, for a total of 40 mg/day of ifenprodil tartrate. The time schedules of the study are provided in Table 2. These interventions were done for 4 weeks and the patients were assessed at the previous observation date (VISIT1), the administration start date (VISIT2), each 2 weeks (VISIT 3 and 4) and followed up for 4 weeks (VISIT5).

Table 2
Time schedules of this study.

| VISIT date | Previous observation period | Administration Period | Post observation period |
|------------|----------------------------|-----------------------|-------------------------|
| Period     | VISIT 1                    | VISIT 2 Administration start date | VISIT 3 | VISIT 4 | VISIT 5 |
| Consent form | 1—28 days                  | 0 week                | 2 weeks | 4 weeks | 4 weeks later |
| person him/herself and legally acceptable representative | □ | □ | ■ | ■ | □ |
| Patients background confirmation | □ | □ | ■ | ■ | □ |
| Height | □ | □ | ■ | ■ | □ |
| Body weight | □ | □ | ■ | ■ | □ |
| Vital signs | □ | □ | ■ | ■ | □ |
| Diagnostic items | □ | □ | ■ | ■ | □ |
| DSM-IV-TR | □ | □ | ■ | ■ | □ |
| M.I.N.I.-kid | □ | □ | ■ | ■ | □ |
| Study drug administration | □ | □ | ■ | ■ | □ |
| Medication situation confirmation | □ | □ | ■ | ■ | □ |
| Effective assessments IES-R-J | □ | □ | ■ | ■ | □ |
| TSCC-J | □ | □ | ■ | ■ | □ |
| CDRS-R | □ | □ | ■ | ■ | □ |
| DSRS-C-J | □ | □ | ■ | ■ | □ |
| CGI-PTSD-S | □ | □ | ■ | ■ | □ |
| CGI-PTSD-I | □ | □ | ■ | ■ | □ |
| CGI-PTSD-I | □ | □ | ■ | ■ | □ |
| Serum | □ | □ | ■ | ■ | □ |
| biomarkers | □ | □ | ■ | ■ | □ |
| Safety assessments Adverse events | □ | □ | ■ | ■ | □ |
| Blood test | □ | □ | ■ | ■ | □ |
| Urine test | □ | □ | ■ | ■ | □ |

□: Before study drug administration ■: After study drug administration.
VISIT 1 and VISIT 2 is possible even on the same day.
2.5. Primary outcome measures

For the primary outcome measure of the study, we used the patients’ Impact of Event Scale-Revised Japanese Version (IES-R-J) scores with the time frame of changes from the baseline IES-R-J total score at 4 weeks. The retest reliability and internal consistency of the IES-R-J have been established (Asakura et al., 2002). Individuals with PTSD and partial PTSD have shown significantly higher scores compared to non-PTSD cases. The IES-R-J can be a particularly useful self-rating diagnostic instrument particularly for survivors with PTSD symptoms as a clinical concern (PTSD + partial PTSD) by using a 24/25 cutoff for the total score.

2.6. Secondary outcome measures of clinical symptoms

For the secondary outcome measures of the patients’ clinical symptoms, we assessed the IES-R at the time frame based on changes from the baseline IES-R total score at 2 weeks, changes from the baseline IES-R intrusion subscore, avoidance subscore and hyperarousal subscore at 2 and 4 weeks; the Trauma Symptom Checklist for Children Japanese Version (TSCC-J) (Murata et al., 1996) total score; the Depression Self-Rating Scale for Children Japanese Version (DSRS-C-J) (Poznanski et al., 1984) total score; the Depression Rating Scale for Children Japanese Version (DRSRS-C-J) (Murata et al., 1996) total score; and the Clinical Global Impressions Improvement scales and Severity scales (Busner et al., 2007) for PTSD (CGI-PTSD-I, CGI-PTSD-S) at the time frame based on changes from the baseline scores at 2 and 4 weeks. The TSCC-J measures post-traumatic stress and related psychological symptomatology in children ages 8–16 years who have experienced one or more traumatic events, such as physical or sexual abuse, major loss, or natural disasters, or who have been a witness to violence. The 54-item TSCC-J includes two validity scales (under-response and hyper-response), six clinical scales (anxiety, depression, anger, posttraumatic stress, dissociation, and sexual concerns), and eight critical items. The CDRS-R is a brief rating scale based on a semi-structured interview with the child (or an adult informant who knows the child well). Designed for 6–12-year-olds, the CDRS-R has also been meaningfully used with adolescents (Poznanski et al., 1984 Stallwood et al., 2021). The interviewer rates 17 symptom areas (including those that serve as DSM-IV criteria for a diagnosis of depression). The DRSRS-C-J is easy to use and has a predictive value comparable to that of a psychiatric global rating of depressed appearance and history of depression. There was confirmation that the DRSRS-C-J can tap an internal dimension of depression and that children are able to evaluate their feeling states. The CGI-PTSD-I is a 7-point scale that requires the clinician to assess how much the patients’ PTSD has improved or worsened relative to a baseline state at the beginning of the intervention. The scale is rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. The CGI-PTSD-S is also a 7-point scale that requires the clinician to rate the severity of the patients’ PTSD at the time of assessment, relative to the clinician’s past experience with patients who have the same diagnosis. Considering the total clinical experience, a patient is assessed on the severity of mental illness at the time of rating as follows: 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill. The PTSS patients’ in this study were evaluated by an experienced child psychiatrist (Tsai, So) after the administration of the Mini-International Neuropsychiatric Interview for children and adolescents (MINI-KID) (Sheehan et al., 2010).

2.7. Safety and adverse event

We assessed each patient’s result on blood tests and urine analyses at VISIT1 and at VISIT4. The blood tests included red blood cells (RBC), mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), leukocytes (WBC), hemoglobin (Hb), hematocrit (Ht), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GTP), creatine phosphokinase (CPK), uric acid (UA), blood urea nitrogen (BUN), creatinine, total protein, albumin, sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), total cholesterol, triglyceride, blood sugar level, thyroid-stimulating hormone (TSH, only VISIT1), free triiodothyronine (FT3, only VISIT1), and free thyroxine (FT4, only VISIT1). The urine analyses included specific gravity, protein qualitative, sugar qualitative, occult blood reaction, and a pregnancy test if suspected. We assessed each patient’s height, body weight, vital signs (body temperature, pulse rate, diastolic blood pressure [DBP] and systolic blood pressure [SBP]) and any of adverse events at all VISIT except height (only VISIT 1) (Table. 2).

2.8. Statistical analyses

The statistical analyses and reporting of this trial were conducted in accordance with the Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online TeleHealth (CONSORT-EHEALTH) guidelines (Eysenbach, 2011). In preliminary research (Rash et al., 2008), the mean IES-R-J total score of adult patients with PTSD was approx. 45 (SD = 18). Our previous ifenprodil treatment PTSD case studies (Kishimoto et al., 2012; Sasaki et al., 2013) revealed the improvement of adolescent and adult PTSD symptoms, and we speculated that ifenprodil treatment would be clinically effective if the IES-R total score is lowered by 12 points in the medication group compared to the placebo group. We thus hypothesized that to observe a 12-points decrease on the IES-R-J total score (SD = 15) between the placebo and ifenprodil groups, we would need to calculate the necessary number of cases to meet a significance level on two sides at 5% and detection power at 90%; the calculated value was 34 patients. We therefore first set 20 patients per each group (40 total) as the target number of cases in consideration of a dropouts. The demographic data of the patients were summarized, and for continuous measurements, the mean ± standard deviation (SD) or median (interquartile range) were tabulated. For categorical measurements, the frequencies and percentages were computed. In the primary analysis, changes in the IES-R-J total score from the baseline to 4 weeks were analyzed using a mixed-effect model, with ‘patient’ as a random factor and ‘time’ (2 and 4 weeks) and ‘group’ (including the interaction factor) and a baseline values as fixed factor. For pairwise between-group comparisons at the different time points, the significance criterion is set to 0.025 to account for multiplicity by the Bonferroni method. Additionally, we controlled the secondary outcomes using the false discovery rate (FDR) calculations to adjust for multiple testing (q-value < 0.15). We analyzed the secondary outcomes using a similar approach (mixed-effect models) as primary analyses. In the safety analysis, the frequencies and percentages of adverse events were computed. Tests were two-tailed, and p-values <0.05 were accepted as significant. Statistical analyses were performed using the SAS statistical software package, ver. 9.4 (SAS Institute, Cary, NC, USA).

2.9. Trial registration

We registered this trial on the official database of clinical research (ClinicalTrials.gov) (Chiba University 2013a) as NCT01835093 on July 11, 2013 and on the UMIN clinical trial registry (Chiba University 2013b) as UMIN000011720 on September 11, 2013.

3. Results

The recruitment of subjects began on January 21, 2014 and was
suspended in March 2019 due to low recruitment. We randomized the 10 patients (one male, nine females) into two arms: those receiving placebo (n = 4) or 40 mg/day ifenprodil tartrate (n = 6) for 4 weeks (Table 3). The baseline demographic and clinical characteristics of the 10 adolescent patients with PTSD are summarized in Table 4. Six patients were drug naïve. The other four patients had received drugs before entering the trial (n = 1 each): olanzapine 10 mg/day; lithium 800 mg/day; lithium 600 mg/day + aripiprazole 3 mg/day; and olanzapine 5 mg/day + valproate acid 800 mg/day. Treatment with these drugs was stable for the 4 weeks prior to enrollment, and was stable during the trial.

All of the patients were assessed by the IES-R-J (the primary outcome measure) and the TSCC-J, CDRS-R, DSRS-C-J, CGI-PTSD-I and CGI-PTSD-S; their body weight and vital signs (changes from baseline at 2 and 4 weeks Table 5) and urine and blood test results (changes from baseline at 4-weeks) were also examined. The adverse events are listed in Table 5: there were no severe adverse events. Both the placebo and Ifenprodil tartrate were well tolerated, with no patients discontinuing interventions because of side effects. No significant effect was revealed in blood test, urine test, body weight, or vital signs other than DBP.

The baseline scores and mean changes of the primary and secondary outcomes are shown in Table 6. The comparison of the two groups’ baseline IES-R-J total scores and 4-week end-point scores revealed a mild trend of improvement (p = 0.0895), and the difference was −9.314 (95% confidence interval [CI]: −20.50, 1.867). A comparison of baseline scores and 2-week intermediate-point scores (secondary outcome measure) showed the IES-R-J hyper arousal subscore (p = 0.0165, FDR <0.15), TSCC-J dissociation subscore (p = 0.0169, FDR <0.15) improved significantly. The comparison of baseline TSCC-J sexual concerns subscores and 2-week (p = 0.0150, FDR <0.15) and 4-week (p = 0.0150, FDR <0.15) end-point scores revealed significant improvements in the ifenprodil-treated patients. A comparison of baseline scores and 2-week intermediate-point scores (secondary outcome measure) showed the IES-R-J total score (p = 0.0398) and TSCC-J anxiety subscore (p = 0.0485) revealed a mild trend of improvement (Fig. 2, Table 6). However

4. Discussion

The results of our analyses demonstrated that ifenprodil was significantly more efficacious than placebo at treating PTSD symptoms at 2-weeks — especially hyperarousal symptoms as measured on the self-rated IES-R-J, and the dissociation symptoms and sexual concerns symptoms as measured on the self-rated TSCC-J. Ifenprodil also produced significant improvement over placebo as measured on the self-rated TSCC-J sexual concerns symptoms at 4 weeks. Although, other clinical rating scales (CDRS-R, DSRS-C-J, CGI-PTSD-S and CGI-PTSD-I) showed no significance, a comparison of baseline IES-R-J total scores and 4-week primary end-point scores showed a mild trend of improvement and the difference score was −9.314. No serious adverse event was reported in either group, and all patients completed the study.

To our knowledge, this is the first report demonstrating the beneficial effect of ifenprodil in treating adolescent PTSD subjects in a randomized, double-blind, placebo-controlled trial method. Although a comparison of baseline IES-R-J total scores (primary outcome measure) and 4-week end-point scores showed a mild trend of improvement, maintenance of the improvement in VISIT2 (2 W) is not accomplished. Therefore, Ifenprodil might not have the prolonged effect for adolescent PTSD symptoms. However, this may be due to the small sample size used in the study and these findings suggest that further, higher-powered studies will be necessary to establish the potential utility of ifenprodil in PTSD.

We firstly planed 40 participants at Chiba university Hospital. However, it is difficult to recruit because of the difficulty of obtaining consent to adolescent subjects and legally acceptable representative. A systematic review showed that the commonly assessed predictors of recruitment and retention can be categorised into parent characteristics, child characteristics, family characteristics and neighbourhood characteristics (Robinson et al., 2016). For adolescent PTSD patients, it takes courage to state the background of their symptoms. So it is important to make it easier for them to receive medical examinations by raising awareness about PTSD symptoms.

We also suggested that difficulties exist in coordinating and operating global, multicenter studies that include pediatric populations, possibly due to differences in regulations or administrative procedures across regions. There are several aspects to be considered and addressed, such as developing support systems for clinical trials and improving infrastructure or funding systems (Tanemura et al., 2021). In Japan, the Specified Clinical Research Law was started in April 2018, and the accreditation examination fee of the Certification of Clinical Trials

| Table 4 | Baseline demographics and clinical characteristics. |
|---|---|
| | Ifenprodil (n = 6) | Placebo (n = 4) |
| Gender * | Male | 1 (16.7) | 0 (0) |
| | Female | 5 (83.3) | 4 (100) |
| Age, years b | 14.2 (1.6) | 14.3 (1.9) |
| Height, cm b | 155.0 (5.5) | 157.7 (2.9) |
| Duration of PTSD symptoms, months c | 37.5 (7 - 67) | 18.0 (14.5 - 22) |

* Data are expressed as number (%).  
** Mean (SD).  
† Median (IQR).  
‡ Number of subjects and drug name (Dose, mg/day).
Table 6
The baseline scores and mean changes of the primary and secondary outcomes.

| Item | Ifenprodil (n = 6) | Placebo (n = 4) | Difference (95% confidence interval) | Difference (95% confidence interval) |
|------|--------------------|----------------|--------------------------------------|--------------------------------------|
|      | Mean baseline (SD) | Mean change from baseline (SD) | Mean change from baseline (SD) | Mean change from baseline (SD) | Mean change from baseline (SD) | Mean change from baseline (SD) | P value | 2W: VISIT3 | 4W: VISIT4 |
| IES-R J total scale score | 54.83 (15.45) | 0.833 (3.371) | 5.667 (7.202) | 58.00 (19.44) | 11.000 (10.985) | 3.500 (5.802) | 0.167 | | | −11.98 (−23.22, −0.739) |
| IES-R J intrusion subscale score | 21.50 (9.03) | −1.500 (2.510) | −1.833 (2.639) | 20.00 (8.98) | 3.000 (5.477) | 1.000 (2.160) | 0.250 | | | −4.600 (−11.10, 1.834) |
| IES-R J avoidance subscale score | 14.83 (3.97) | 1.333 (3.502) | −0.167 (4.622) | 18.75 (9.14) | 6.250 (4.924) | 2.500 (3.512) | 0.134 | | | 0.134 (0.0959, 0.272) |
| IES-R J hyperarousal subscale score | 18.50 (3.39) | −0.667 (1.633) | −3.667 (1.966) | 19.25 (3.10) | 1.750 (1.500) | 0.000 (4.243) | 0.167 | | | −2.988 (−4.463, −0.651) |
| TSCC-J total scale score | 80.67 (42.76) | −9.667 (13.909) | −12.67 (16.415) | 96.75 (36.63) | −0.250 (20.089) | −6.750 (27.403) | 0.167 | | | −14.63 (−31.44, 2.170) |
| TSCC-J underresponse subscale score | 1.33 (2.16) | 0.167 (1.329) | 0.333 (0.186) | 0.250 (0.50) | −0.250 (0.500) | 0.250 (0.500) | 0.167 | | | 0.586 (−1.042, 2.215) |
| TSCC-J hyperresponse subscale score | 1.33 (1.97) | −0.333 (0.516) | −0.167 (0.408) | 2.25 (2.63) | −0.750 (0.500) | −0.500 (1.000) | 0.167 | | | 0.258 (−0.334, 0.850) |
| TSCC-J anxiety subscale score | 16.17 (6.91) | −1.833 (1.329) | −1.833 (2.401) | 18.50 (5.92) | 1.000 (2.449) | −0.500 (6.028) | 0.167 | | | 0.336 (−0.850, 2.508) |
| TSCC-J depression subscale score | 14.00 (8.94) | −0.833 (1.329) | −0.833 (2.483) | 17.50 (5.32) | −1.000 (3.637) | −5.250 (7.089) | 0.167 | | | 0.0485 (0.024, 0.381) |
| TSCC-J anger subscale score | 11.83 (7.36) | −0.667 (4.082) | −2.000 (5.477) | 15.50 (8.50) | −2.000 (4.761) | −1.750 (3.304) | 0.167 | | | 0.516 (−6.051, 7.084) |
| TSCC-J posttraumatic stress subscale score | 19.17 (8.06) | −2.000 (3.286) | −3.000 (5.060) | 21.50 (8.10) | 1.500 (6.191) | −0.750 (6.131) | 0.167 | | | 0.8579 (−4.209, −2.215) |
| TSCC-J dissociation subscale score | 13.33 (8.02) | −1.000 (3.578) | −2.000 (3.286) | 17.25 (11.00) | 1.750 (5.123) | 2.250 (7.455) | 0.167 | | | 0.1416 (−6.279, −1.054) |
| TSCC-J sexual concerns subscale score | 3.50 (5.86) | −3.167 (5.879) | −3.167 (5.879) | 4.00 (3.92) | −0.500 (0.577) | −0.500 (0.577) | 0.167 | | | 0.0169 (−3.066, −0.775) |
| DSRS-C total scale score | 19.83 (9.39) | 0.167 (0.983) | −0.167 (2.041) | 26.75 (3.10) | 1.000 (0.816) | −2.750 (2.754) | 0.167 | | | 0.0244 (−2.367, 2.504) |
| CDRS-R total scale score | 57.83 (11.27) | −2.167 (8.280) | −8.167 (11.303) | 64.75 (13.30) | −7.000 (4.899) | −8.500 (7.234) | 0.167 | | | 0.1678 (8.687, −2.223) |
| CGI-PTSD-S scale score | 6.00 (0.00) | −0.167 (0.408) | −1.000 (0.894) | 6.25 (0.50) | −0.500 (0.577) | −0.750 (0.957) | 0.167 | | | 0.488 (−0.281, 1.257) |
| CGI-PTSD-I scale score | 4.17 (0.41) | −0.167 (0.408) | −1.000 (0.894) | 4.00 (0.00) | −0.500 (0.577) | −0.500 (0.577) | 0.167 | | | 0.1772 (−0.222, −0.609) |
| Body weight (kg) | 50.47 (5.03) | 0.25 (1.23) | −0.12 (1.44) | 54.95 (7.42) | 0.60 (6.30) | 0.65 (1.33) | 0.16 (1−0.15, 1.83) | | | 0.16 (1−0.15, 1.83) |
| Body temperature (°C) | 36.90 (0.35) | 0.10 (0.36) | 0.13 (0.29) | 36.75 (0.19) | 0.10 (0.29) | 0.15 (0.33) | 0.10 (0.34, 0.55) | | | 0.09 (0−0.28, 0.45) |
| Pulse rate (per minute) | 72.00 (12.18) | 13.67 (14.01) | 9.17 (8.33) | 72.75 (5.74) | 2.25 (9.91) | 10.75 (11.76) | 0.133 | | | 0.133 (0.098, 0.268) |
| Systolic blood pressure (mmHg) | 114.50 (8.73) | 6.33 (13.71) | −1.17 (6.43) | 110.00 (10.80) | 4.5 (15.02) | 7.75 (6.13) | 0.14 (19−19.99, 23.83) | | | 0.997 (8.83, 19.07, 1.41) |
| Diastolic blood pressure (mmHg) | 66.83 (8.95) | −3.07 (8.78) | −2.83 (6.68) | 63.75 (8.96) | 4.5 (17.3) | 8.25 (5.91) | 0.16 (15−0.75, 1.63) | | | 0.089 (10.28, −20.19, 0.38) |

The difference of least-square means and 95% confidence interval were estimated using the linear mixed model for repeated measure.

* p < 0.025 and FDR < 0.15.
Review board has required every year. This financial problem is one of the reasons why we could not continue this clinical trial. Therefore, it is also important to support clinicians who can easily conduct international clinical trials in the future with financial support and patient and public involvement promotion activities. In addition, the target age of this study was 13 to 18 years old, and the range was limited, so it is probable that the number of registered participants was small. Potential participants in the clinical setting and parents and/or patients might be in too much distress because they have to be absent from school. Therefore, it may be a solution to include adult subjects in the clinical trials.

There are some limitations. The first limitation of this trial is its small sample size as mentioned above. The second limitation is mood comorbidity of bipolar disorder or depressive disorder. Four subjects had received drugs before entering the trial, namely olanzapine, lithium, lithium and aripiprazole, olanzapine and valproate acid, while six subjects were drug-naive. Although treatment with these drugs was stable for the 4 weeks prior to enrollment and was stable during the trial, we suggest to examine association with the mood disorders comorbidity.

In conclusion, our study suggests that ifenprodil might not have the prolonged effect for adolescent PTSD symptoms, it may prove to be a short-term effective alternative safe treatment for adolescent patients with PTSD. Nonetheless, more randomized, double-blind trials including adult subjects are needed to confirm ifenprodil tartrate’s efficacy.

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CRediT authorship contribution statement

**Tsu*yoshi Sasaki**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Kenji Hashimoto**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Tomihisa Niitsu**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Yutaka Hosoda**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Yasunori Oda**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Masaomi Iyo**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Yuki Shiko**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing, Formal analysis. **Yoshifuto Ozawa**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing, Formal analysis. **Yohei Kawasaki**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing, Formal analysis. **Nobuhisa Kanahara**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Akishi Shiina**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Takaaki Suzuki**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Takeshi Sugawara**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Hideki Hanoka**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Takeshi Sugawara**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing. **Masaomi Iyo**: Visualization, Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

Please confirm attachment of ICMJE. Chiba University funded for this study.

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Fig. 2. Mean change from baseline by 2weeks, Data are expressed as least square mean (SE). *p<0.025 versus placebo.
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