



Open Trial of a Brief Imagery-Based Stabilization Psychotherapy for Adults with Acute Posttraumatic Stress Disorder

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Purpose: Early intervention after trauma is needed for reduction in clinical distress and prevention of chronic posttraumatic stress disorder (PTSD). This study describes findings from an open pilot trial of a brief stabilization psychotherapy based on imagery techniques for adults with acute PTSD (i.e., within 3 months of onset).

Materials and Methods: Four sessions of 60-minute individual psychotherapy were conducted on 18 participants with PTSD within 3 months after accidents, 15 of whom completed the treatment. The clinician-administered PTSD scale for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the Hamilton Depression and Anxiety Rating Scales, and self-questionnaires were administered at pre-treatment, post-treatment, and 6-month follow-up.

Results: Eight (53.3%) of the 15 patients at post-treatment and 8 of the 9 patients at 6-month follow-up did not meet the DSM-5 criteria for PTSD. Reliable change of PTSD symptoms after treatment was observed in 6 of 15 (45.0%) patients at post-treatment and in 4 of 9 (45.0%) patients after 6 months. There was a significant decrease in PTSD, depression, anxiety, and impaired quality of life scores after treatment, and these gains were maintained after 6 months. No cases of exacerbated PTSD symptoms were observed among completers and non-completers.

Conclusion: Our findings suggest that brief stabilization sessions are safe treatment options for acute PTSD (KCT0001918).

Key Words: Posttraumatic stress disorder, psychotherapy, psychological trauma, stabilization

INTRODUCTION

Posttraumatic stress disorder (PTSD) arises when a person is exposed to overwhelming life-threatening experiences, further developing the array of psychological, cognitive, behavioral, and somatic symptoms for more than 1 month.¹ It is not an un-

common disorder in that the mean lifetime PTSD prevalence of 24 different countries was 3.2% (median=2.3%, range=0%–9.2%).² In South Korea, an epidemiological study has reported a life-time PTSD prevalence at 4.2% in general population.³ The long-term cost of the disorder is also noteworthy, as PTSD may persist for years; for a minority, it can last up to decades.⁴ Furthermore, those suffering from continuing PTSD show poor physical and psychological health and low quality of life.⁵

Early intervention a few months after trauma is necessary to reduce ruling distress and prevent long-term effect of the illness. According to clinical practice guidelines from the International Society for Traumatic Stress Studies, trauma-focused cognitive behavior therapy (TF-CBT), cognitive therapy, and eye movement desensitization and reprocessing (EMDR) are recommended as standard therapies for adults with PTSD within the first 3 months of a traumatic event.⁶

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More recently updated Australian guidelines strongly recommend stepped/collaborative care, and conditionally recommend TF-CBT and brief EMDR.⁷ Although emphasis on early psychological interventions has continued in studies,⁸ other international guidelines have not designated acute PTSD (i.e., within 3 months after trauma) as distinct from chronic conditions, probably owing to the exclusion of the acute subtype in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).¹

Despite current studies supporting TF-CBT in general, further development of early interventions is necessary for the following reasons. First, brief treatments are preferred if they are not inferior to the standard established therapies, as TF-CBT studies have administered therapy sessions in the range of five–12 sessions (7.5 to 18 hours).⁸ Second, treatment responses to established treatment, such as CBT, may have room for further improvement. One clinical trajectory analysis noted that CBT did not affect the 1-year course of 73% of individuals with acute stress symptoms.⁹ Third, therapy should be under the “first, do no harm” principle to minimize any exacerbation from treatment. A study found that 14.7%–28.6% of TF-CBT research participants reported exacerbation during treatment.¹⁰ Thus, there exist a continuing need for more efficient and safe early interventions.

Imagery-based psychotherapy can be a good candidate for these purposes. When imagery rescripting was added to conventional exposure therapy, it had less dropouts (25% vs. 51%) than exposure therapy alone.¹¹ In a recent review of clinical trials, the average session number for imagery rescripting was 4.3 (SD=4.6; range 1–16) sessions, indicating fewer sessions for treatment.¹²

Stabilization is also pertinent to immediate or mid-term post-disaster or mass trauma, where the main focus of therapy is to promote safety, calming, a sense of efficacy, connectedness, and hope.¹³ Independent stabilization-focused psychotherapies were developed and pilot-tested: imaginative stabilization group therapy for refugees (40 sessions based on mindfulness and guided imagery),¹⁴ and a stabilization group psychotherapy for acute trauma (a single session based on psychoeducation and imaginative stabilization).¹⁵

We developed a four-session manualized protocol of imagery-based stabilization psychotherapy for adults with acute PTSD,¹⁶ and the current study investigated the reduction in symptoms of PTSD, depression, and anxiety in addition to changes in the quality of life after treatment and 6 months thereafter. We also examined the diagnostic status and treatment response of the participants.

MATERIALS AND METHODS

Participants and procedure

Participants were recruited from referrals from local counsel-

ing centers and clinics, and advertisements were conducted through homepages, mail, and professional organizations, all of which were conducted at Hanyang University Guri Hospital in Gyeonggi-do, South Korea between March 2017 and February 2019. Inclusion criteria were as follows: 1) age between 18 and 70 years, 2) current diagnosis of PTSD or partial PTSD according the Structured Clinical Interview for DSM-5 Disorders (SCID-5),¹⁷ 3) within 3 months after trauma, and 4) ability to communicate in Korean. Exclusion criteria were as follows: 1) intellectual disability, 2) neurocognitive disorders, 3) severe medical conditions, or 4) comorbid psychotic illness.

A total of 30 participants were assessed for eligibility, and 12 were excluded because they failed to meet the DSM-5 criteria for PTSD, leaving a final of 18 participants. Table 1 shows the sociodemographic and clinical variables. Most participants were female (88.9%) and with high school or above education (83.3%). Half (50.0%) of the participants were married, and

Table 1. Baseline Characteristics of Participants (n=18)

Variables	Value
Sex	
Male	2 (11.2)
Female	16 (88.8)
Marital status	
Married	9 (50.0)
Not married	9 (50.0)
Employment	
Employed/students	11 (61.2)
Unemployed/not working	7 (38.8)
Education	
Below high school	3 (16.7)
High school graduate	10 (55.5)
University or more	5 (27.8)
Annual income (US dollars)	
<20000	4 (22.2)
20000–40000	10 (55.6)
>40000	4 (22.2)
Index trauma	
Motor vehicle accidents	12 (66.7)
Witnessed death (loss)	4 (22.2)
Natural disaster	2 (11.1)
Psychiatric comorbidity	
Any	10 (55.6)
Major depressive disorder	8 (44.4)
Panic disorder	2 (11.1)
Personality disorder	1 (5.5)
Psychotropic medication	
Yes	7 (38.8)
No	11 (61.2)
Age (yr)	36.3±13.7
Months after trauma	1.8±0.6

Data are presented as n (%) or mean±standard deviation.

more than half were employed or students (61.2%) or had an annual income of between 20000 and 40000 US dollars (55.6%). The mean age of the participants was 36.3 [95% confidence interval (CI)=29.5–43.1] years, and the mean duration after trauma was 1.8 months (95% CI=1.5–2.1).

Seven (38.8%) participants were taking concurrent psychotropic medication. The dose and types of psychotropic medication remained the same until the post-treatment evaluation, but not during the follow-up period depending on clinical judgement. The most common traumatic event was motor vehicle accidents (n=12, 66.7%), followed by witnessing death of loved ones by suicide or accidents (n=4, 22.2%), and natural disaster (n=2, 11.1%). Ten of the 18 participants (55.6%) had at least one psychiatric comorbidity: major depressive disorder (n=8, 44.4%), panic disorder (n=2, 11.1%), or personality disorder (n=1, 5.5%).

Participants were assessed at three time frames: initial assessment was usually performed at 1 week before treatment (T0), 1 or 2 weeks after treatment (T1), and 6 months after treatment completion (T2). Thus, the time gap between T0 and T1 was 5 weeks, and 6 months between T1 and T2. The assessment interview lasted for approximately 90 minutes, with an average of 60 minutes for the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5),¹⁸ the Hamilton Depression Rating Scale (HDRS),¹⁹ and the Hamilton Anxiety Rating Scale (HARS)²⁰ by either a clinical psychologist or psychiatrist.

A flowchart of the study process is shown in Fig. 1. As 3 par-

ticipants dropped out prematurely (16.7% attrition rate), 15 participants who completed four sessions of intervention were assessed at T1, and 9 of the 15 (60.0%) were followed up after 6 months (T2). This study was approved by the Research Ethics Board of Hanyang University Guri Hospital (IRB No. 2015-05-012), and the clinical trial protocol was registered with the Clinical Research Information Service (KCT KCT0001918). Each participant provided written informed consent. Participants received an imbursement corresponding to 150 US dollars.

Measures

SCID-5

The SCID-5 was used to confirm the current diagnosis of PTSD and other comorbid psychiatric disorders.¹⁷ In addition to PTSD and acute stress disorder, the SCID-5 assesses mood, psychotic, substance use, anxiety, obsessive compulsive, attention deficit/hyperactive, and adjustment disorders.

CAPS-5

The CAPS-5 is a 30-item semi-structured interview that has been regarded as the golden standard for the diagnosis of PTSD and assessment of symptom severity. After recognizing exposure to an index traumatic event, the interviewer can infer a current (over a month) or lifetime diagnosis of PTSD according to the DSM-5 diagnostic criteria.¹⁸ The total scores or number of existing symptoms are often used to assess the overall

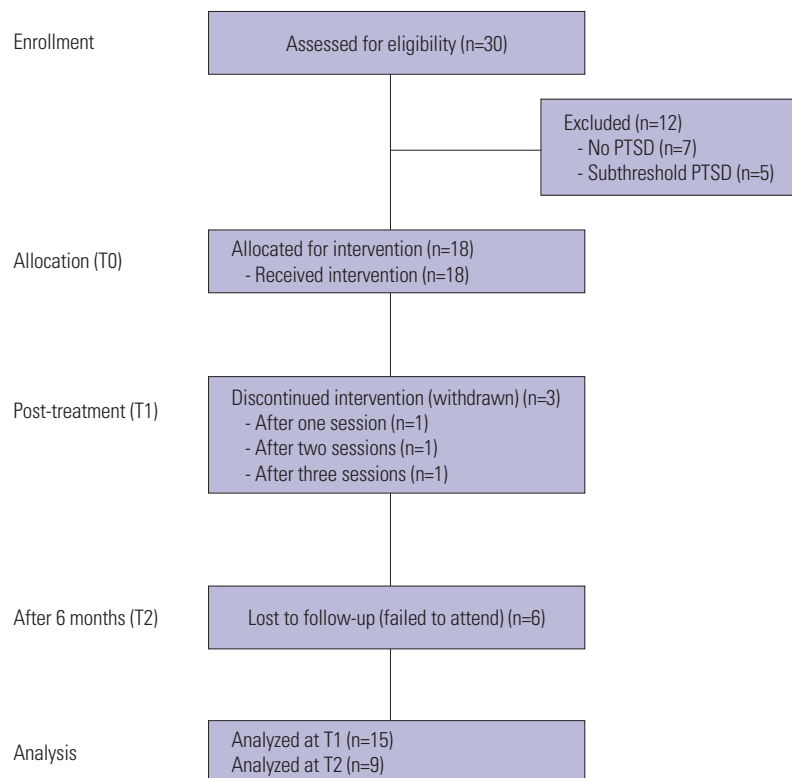


Fig. 1. Flowchart of participant progress. PTSD, posttraumatic stress disorder.

intensity of an illness. This scale has demonstrated good psychometric properties.¹⁸

HDRS

The HDRS is a 17-item rater-administered scale that measures the severity of depressive and changes over time. The items of the HDRS are rated on 5 (0–4) or 3-point (0–2) scale; thus, total scores lie in the range between 0 and 54.¹⁹

HARS

The HARS is a 14-item clinician interview scale that is used to measure anxiety. Each item is measured on a 5-point (0–4) scale, with total scores ranging from 0 to 56.²⁰

PTSD Checklist for DSM-5

The PTSD Checklist for DSM-5 (PCL-5) is a 20-item self-report questionnaire that assesses each criterion of the DSM-5 PTSD symptoms during the last month. Likert type responses range from 0 (not at all) to 4 (extremely); thus, total score ranges between 0 to 80.²¹

Beck Depression Inventory, Second Edition

The Beck Depression Inventory, Second Edition (BDI-II) is a 21-item self-questionnaire that assessed the severity of depression during the last 2 weeks. Respondents are asked to choose 1 of the 4 statements (0–3) about symptoms of depression, with increasing severity in descending order; thus, each score adds up to a total score ranging from 0 to 63.²²

Beck Anxiety Inventory

The Beck Anxiety Inventory (BAI) is a 21-item self-reported questionnaire that is used to assess the severity of anxiety, with total scores ranging from 0 to 63.²³ Each item has four responses, and the respondents are asked to choose from “not at all” (0) to “severely or bothered a lot” (3) to indicate how much they were bothered by the symptom during the last month.

Short Form 12 Health Survey

The Short Form 12 Health Survey (SF-12) scale is a shorter version of Short Form-36 Health Survey, version 2, which is the most popular instrument for assessing health-related quality of life. The items in the SF-12 cover perceived quality of life in general, physical and mental health, and social functioning.²⁴

Intervention

The participants received four consecutive weekly sessions of individual psychotherapy. Each session lasted 60 minutes, and was conducted by one of the two clinical psychologists and a psychiatrist. The protocol was developed based on the stabilization stage of phased trauma therapy¹¹ and the principles of early intervention after trauma.¹² Overall, the program encompassed psychoeducation, coping skills training, imagery work to reduce trauma symptoms, and resource building. Session 1

comprised 1) psychoeducation about trauma, reaction, meaning, course and treatment (20 minutes); 2) identifying external or internal triggers that cause intrusive memory and distress and how to deal with them (20 minutes); and 3) teaching and rehearsing somatosensory grounding to stay in the present time and space through mindfulness to visual, auditory, tactile sensation, and motor movement (20 minutes). Session 2 included 1) containment exercise (30 minutes), where visual imagery was created to reduce distress and enhance self-controlling capacity, and 2) a positive treatment goal (30 minutes) that involved future imagery development to foster motivation for treatment and a positive outlook.²⁵ Session 3 consisted of 1) resource imagery, in which participants developed empowering imagery for successful coping from their personal experiences or supportive figures, modified from Resource Development and Installation²⁶ and 2) distancing imagery technique, visuospatial modification of intrusive images, or flashbacks to reduce distress from intrusive symptoms and enhance self-control capability.¹⁶ In the final session (Session 4), modified imagery rehearsal therapy was performed for nightmares or intrusive imagery to gain control over trauma-related dreams or intrusion.²⁷ Table 2 shows a summary of the four sessions, and a detailed description of the session, including therapist’s verbatim ac literatim, can be found in the therapists’ protocols.¹⁶

Operational definitions

Diagnostic status

When participants no longer met the diagnostic threshold of PTSD (i.e., number of symptoms required for B, C, D, or E clusters), it was defined as “loss of PTSD diagnosis.” When the total score of the CAPS-5 was ≤ 8 , it was considered “complete remission.”²⁸

Treatment response

Treatment response was investigated using two standards: 1) more than 30% decline from baseline PTSD scores;²⁹ and 2) “reliable change” (reduction of 12 scores or more from the initial PTSD scores of CAPS-5).²⁸

Data analysis

Data were analyzed using SPSS 25 for Windows (IBM Co., Armonk, NY, USA). We conducted paired t-tests for change in symptoms and Hedges’g calculations for the effect size. Hedges’g was used instead of Cohen’s d since it provided a better estimate in a small sample.³⁰ Statistical significance was set at $\alpha = 0.05$ (two-tailed).

Table 2. Contents of a Four-Session Imagery Stabilization Therapy

Protocol component	Minutes	Description
Session 1		
Psychoeducation	20	Providing information on trauma and posttraumatic reactions
Identification of triggers	20	Identification of external and internal triggers causing intrusion or distress
Grounding exercise	20	Teaching skills to stay at present time and space through sensory or motor modalities
Session 2		
Containment exercise	30	Creating visual imagery for containing posttraumatic distress
Positive treatment goal	30	Development of positive future image and enhancement of sensory elements of the imagery
Session 3		
Resource imagery	30	Building empowering imagery for successful coping from their personal experiences or supportive figure
Distancing imagery	30	Visuospatial modification of intrusive image or flashback to reduce distress from intrusion
Session 4		
Modified imagery rehearsal therapy	60	Imagery modification of nightmares or intrusive image and rehearsal of newly developed substituted imagery and its contexts

Table 3. Means, Standard Deviations, and Summary Statistics for Outcome Measures

	Time 1 (n=15)	Time 2 (n=15)	Time 3 (n=9)	Time 1 vs. Time 2				Time 2 vs. Time 3			
				t	df	p value	Hedges' g	t	df	p value	Hedges' g
CAPS	31.0 (8.8)	19.9 (9.1)	11.8 (3.9)	8.2	14	<0.001	1.24	1.7	8	0.123	0.53
HDRS	17.7 (4.9)	12.3 (6.1)	11.6 (10.8)	4.3	14	<0.001	0.97	0.4	8	0.690	0.14
HARS	20.9 (5.4)	13.8 (6.0)	11.8 (7.0)	7.1	14	<0.001	1.24	0.8	8	0.468	0.28
PCL-5	49.1 (16.0)	31.0 (20.4)	30.6 (29.3)	5.4	12	<0.001	0.59	-0.3	6	0.744	0.05
BDI-II	28.5 (10.0)	20.4 (12.4)	20.9 (18.1)	2.9	13	0.012	0.72	0.1	7	0.917	0.02
BAI	27.6 (12.5)	18.4 (11.5)	19.8 (19.3)	3.2	13	0.007	0.77	-0.7	7	0.503	0.12
SF-12	32.1 (6.4)	25.5 (5.5)	22.8 (8.2)	5.1	13	<0.001	1.11	1.0	7	0.371	0.23

CAPS, Clinician-Administered PTSD Scale; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; PCL-5, PTSD Checklist-5; BDI-II, Beck Depression Inventory-Second Edition; BAI, Beck Anxiety Inventory; SF-12, The Short Form 12 Health Survey.

RESULTS

Attrition and exacerbation

Three participants (16.7%) terminated prematurely, and the number of sessions they attended and reasons for attrition were as follows: one after the first session (lack of gain), one after two sessions (work-related lack of time), and the other after three sessions (moving out of town). In all cases, further intention-to-treat analysis was infeasible; however, no incidence of worsening symptom was reported. Among the 15 completers, none of the CAPS-5 scores increased after treatment, and the range of CAPS-5 reduction was between 1 and 20 (Supplementary Table 1, only online).

Post-treatment evaluation

Change in objective measures

Table 3 illustrates the overall results at baseline, post-treatment, and 6-month follow-up. Changes in the symptoms of PTSD, anxiety, and depression were significantly reduced after treatment, as examined by objective measures. The effect sizes were large for PTSD symptoms according to the CAPS-5 (Hedges' $g=1.24$), anxiety according to the HARS (Hedges' $g=1.24$), and de-

pression according to the HDRS (Hedges' $g=0.97$). The CAPS-5 score was reduced by a mean of 37% (95% CI 26.9–47.6), and no participant had increased CAPS-5 score at T1.

Change in subjective measures

PTSD, anxiety, and depressive symptoms also decreased significantly after treatment, as determined by subjective measures. The quality of life was increased significantly after treatment. Effect sizes were medium for PTSD symptoms on the PCL-5 (Hedges' $g=0.59$), anxiety on the BAI (Hedges' $g=0.77$), and depression on the BDI-II (Hedges' $g=0.72$). The subjective quality of life assessed using the SF-12 improved after treatment with a large effect size (Hedges' $g=1.11$).

Clinical significance

Eight (53.3%) patients did not meet the DSM-5 criteria for PTSD at post-treatment; 1 patient (6.7%) reached a level of complete remission. Reliable change in PTSD symptoms (≥ 12 CAPS-5 score reduction) were observed in 6 of the 15 (45.0%) patients. Nine of the 15 (60.0%) patients were treatment responders defined by $\geq 30\%$ decrease in CAPS-5 scores.

Follow-up after 6 months

Change in measures

Regarding the scores of both objective and subjective instruments, there were no statistically significant differences between T1 (post-treatment) and T2 (after 6 months). The effect size of the CAPS-5 difference between the intervals was medium but not statistically significant (Hedges' $g=0.53$, $p=0.123$).

Clinical significance

Of the nine patients assessed after 6 months, one still met the DSM-5 criteria for PTSD, and four of the five with a PTSD post-treatment further lost their PTSD diagnosis. Two patients (22.2%) reached a level of complete remission. One patient was no longer completely remitted at T2 despite continuing non-diagnosis.

DISCUSSION

The primary goal of this study was to examine the effect of a newly developed stabilization intervention on PTSD status and posttraumatic symptoms in individuals within 3 months after trauma. After completing four weekly individual sessions consisting of psychoeducation, grounding skills, and imagery stabilization and change techniques, approximately half of the participants no longer met the diagnosis of PTSD.

The percentage of loss of PTSD diagnosis after completing trauma-focused psychotherapy in the study showed an average 50%–70% (e.g., 41%–95% for prolonged exposure, 30%–97% for cognitive processing therapy, and 61%–82% for CBT); thus, our finding of 53.3% was comparable but in the lower range of treatment response in the studies.³¹ Overall, the effect sizes of pre- to post-treatment PTSD symptoms were smaller than those of the trauma-focused CBT: average 1.27 (95% CI=0.80–1.74) with self-report and 1.89 (95% CI=1.66–2.12) with observer-rating.³² However, the brief nature of our therapy should be considered in that a full course of CBT (12 sessions or more) from the second month after trauma was superior to the control, whereas shorter course (four to six sessions) of CBT was not superior to repeated assessments.³³

It should also be noted that the symptoms of PTSD may reduce naturally over time; as seen in a small prospective study on survivors of motor vehicle accident, 55% of those diagnosed with acute PTSD had remitted, at least in part, by 6 months.³⁴ However, according to a previous study on patients with traumatic injury, the rate of PTSD at 3, 12, and 24 months after injury remained constantly over time.³⁵ Furthermore, in this study, it is unlikely that post-treatment gains are due to natural recovery, as change within 6 weeks between the pre- and post-treatment assessments are robust and are maintained after 6 months.

We found significant reduction in depression and anxiety,

and improvement in health-related quality of life with medium-to-large effect sizes. Specifically, large effect was observed in clinician-rated anxiety and depression along with self-reported quality of life. Participant-reported anxiety and depression had moderate effects. In a review of PTSD treatment studies within 3 months after trauma, anxiety, and depression were significantly reduced in approximately half of the trials.⁸ As these constructs frequently accompany PTSD either as comorbid disorders or as subsyndromal symptoms,³⁶ the improvement observed in our study is noteworthy. Also, increased perceived quality of life added to the benefits of this intervention. Functional impairment is a significant psychosocial burden in individuals with PTSD and is often neglected in studies on PTSD treatment.³⁷

To date, the use of brief therapy (usually <4.5 hours) for early intervention is not supported by the literature as most studies have used the standard protocol of TF-CBT, except for EMDR, which is conducted for 45 minutes to 3 hours and structured writing therapy that lasts three to five sessions.⁸ Imagery-based PTSD treatments, such as imagery rescripting and imagery rehearsal therapy, require fewer sessions to achieve therapeutic outcomes. Raabe and her colleagues noted that stand-alone imagery rescripting required fewer sessions than combined sequential treatment (18 sessions vs. 26 sessions) for PTSD caused by childhood abuse.³⁸

Our therapy procedure did not involve memory processing (exposure to traumatic memories), and it did not support the conventional view that the emotional processing of traumatic memories is an essential element of trauma therapy. Likewise, non-trauma-focused psychotherapies, such as present-centered therapy, interpersonal psychotherapy, and cognitive therapies without exposure, are known to be effective for PTSD.⁷ As mentioned in the introduction, recently added imagery-based stabilization therapies were also safe and effective for chronic PTSD, and our findings expanded the use of these techniques in the acute phase of PTSD along with previous application to the acute phase of trauma (within 1 month) with acute stress symptoms.¹⁵

Dropout and exacerbation rates are two crucial facets of the safe delivery and acceptance of trauma therapy. In the current study, 15.6% of the participants were lost before completing the four sessions, and no substantial exacerbation of PTSD symptoms was observed. One meta-analytic review found pooled rate of 16% (95% CI 14%–18%) dropout in PTSD studies; however, they failed to note the reason for the dropouts.³⁹ In a small descriptive study of exacerbations among participants from two PTSD trials, dropouts experienced symptom worsening twice as much as treatment completers.¹⁰ Our study reported similar dropout rates as those of previous studies; however, no one had terminated the treatment due to the worsening of his or her condition. In addition, none of the participants reported an increase in PTSD symptoms; this is noteworthy in that cognitive therapy without exposure contents has an exacerbation

rate of 10%–14.7%, while prolonged exposure therapy has the rate between 12.8%–28.6%.¹¹ It is still debated whether exposure to traumatic memory increases the likelihood of PTSD exacerbation, although it is generally accepted that a minority of individuals with PTSD experience exacerbation at least temporarily.¹⁰

This study had several limitations, including a non-controlled design, lack of repeated baseline observation for change before initiation of therapy, and a small sample size; therefore, caution is required when generalizing the results of this study. Additionally, most participants had non-interpersonal single accident-trauma; those with these types of trauma had better outcomes than those with repeated interpersonal or childhood trauma.¹¹

Overall, our findings support the safety and effectiveness of brief imagery-based stabilization techniques in acute PTSD. Future studies are required to expand our findings through well-designed randomized clinical trials with various populations with PTSD, as well as head-to-head comparisons with established trauma-focused psychotherapies.

AUTHOR CONTRIBUTIONS

Conceptualization: Daeho Kim, Hyunji Lee, and Ji Young Min. **Data curation:** Daeho Kim, Hyunji Lee, and Ji Young Min. **Formal analysis:** Daeho Kim, Hyunji Lee, and Jiyoung Hong. **Funding acquisition:** Daeho Kim. **Investigation:** Daeho Kim, Hyunji Lee, and Ji Young Min. **Methodology:** Boyoung Son and Daeho Kim. **Project administration:** Daeho Kim. **Resources:** Daeho Kim. **Software:** Daeho Kim and Jiyoung Hong. **Supervision:** Daeho Kim. **Validation:** all authors. **Visualization:** Daeho Kim and Jiyoung Hong. **Writing—original draft:** Boyoung Son and Daeho Kim. **Writing—review & editing:** all authors. **Approval of final manuscript:** all authors.

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