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Case report

Efficacy of combined subanesthetic ketamine infusion and cervical sympathetic blockade as a symptomatic treatment of PTSD/TBI in a special forces patient with a 1-year follow-up: A case report

Eugene Lipov [a,*], Zubin Sethi [b], Guriqbal Nandra [c], Christopher Frueh [d]

[a] Stella Center, Chicago, United States
[b] Midwestern University Chicago College of Osteopathic Medicine, United States
[c] IV Solution & Ketamine Centers of Chicago, United States
[d] Department of Psychology, University of Hawaii, Hilo, HI, United States

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ABSTRACT

Co-occurrence of posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI) symptoms are particularly prevalent in the special operations forces' community, along with other related conditions (e.g., endocrine dysregulation, sleep disorders, chronic pain). Ketamine infusion (KI) has been shown to increase neuroplasticity as well as memory improvement and cervical sympathetic block (CSB) has been shown to improve cognitive function, reduce sympathetic overactivity, and improve other symptoms of PTSD. We want to report the efficacious use of a single intervention consisting of bilateral CSB technique with subanesthetic KI X5 in a Special Operations Forces patient, diagnosed with PTSD with comorbid TBI, evaluated during treatment and at 1-year follow-up. We postulated KI and CSB would have a synergistic effect. Our patient received KI starting at 0.5 mg/kg, which was escalated daily. KI was combined with right-sided ultrasound-guided CSB (C6 and C4 levels). This was followed the next day by left-sided CSB and KI. Patient's PTSD symptoms were evaluated using the Posttraumatic Stress Disorder Checklist (PCL-5), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), suicidal ideation and other related factors by Concise Health Risk Tracking Self Report (CHRTSR). All measures were assessed prior to treatment, during treatment, and 394 days after. KI combined with CSB showed immediate and prolonged benefits 394 days later regarding the symptoms of PTSD, anxiety, depression, suicidal ideation, and cognitive deterioration (patient report). KI combined with CSB can markedly reduce symptoms of PTSD, psychiatric comorbidities, and cognitive dysfunction.

1. Introduction

Special Operations Forces (SOF) personnel constitute the most elite members in the U.S. military. Compared to conventional forces, SOF personnel typically have longer military careers and are exposed to a greater number of combat deployments, heavy combat experiences, and traumatic brain injury (TBI)-producing exposures that are associated with an increased prevalence of PTSD [1]. SOF personnel are likely to suffer from TBI due to breaching (the use of explosives in close quarters), use of explosives in battle and training, and jumping from airplanes [2]. Dr. Carr's report of blast-induced impairment of cognition among individuals subjected to sustained

* Corresponding author.
E-mail address: elipovmd@aol.com (E. Lipov).

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repetitive blast exposure, such as breaching instructors, is consistent with the above [3]. Prior reports demonstrate that in general, military veterans with TBI are more likely to have comorbid neuropsychiatric issues, including PTSD, depression, anxiety, cognitive impairment, and suicidality [4]. SOF personnel commonly show a unique pattern of interrelated medical, psychological, and social conditions that include TBI, sleep disorders, chronic pain, psychological problems, and others [5]. Current treatments demonstrate limited efficacy in addressing the unique neuropsychiatric symptoms in SOF members and veterans [6].

Current PTSD treatments have focused on psychotherapy or medication, with an unfortunately high drop-out rate, commonly 30%–40% in randomized clinical trials (RCTs). The recovery rate of 60%–80% among treatment completers declines to around 40% in intent-to-treat analyses [7]. Much has been published regarding PTSD treatment efficacy, however, surprisingly little has been reported for TBI treatment efficacy.

TBI and PTSD present with common neuropsychiatric symptoms including anxiety, irritability, insomnia, personality changes, and memory problems, and this overlap complicates diagnostic differentiation. It logically follows that SOF personnel should be treated simultaneously for PTSD and TBI with the most effective methods available. Two relatively new applications of previously used therapies, ketamine infusion (KI) and cervical sympathetic block (CSB), seem to offer much needed hope.

1.1. KI and CSB

Subanesthetic KI is known to alter hippocampal cell proliferation following TBI, which is a possible benefit from KI following TBI in mice [8]. Dr. Browne suggested that ketamine may be effective for treating complications that emerge after blast injury [9]. Dr. Liriano reported immediate, but transient, improvements of PTSD symptoms lasting 1–2 weeks using KI [10]. Stellate Ganglion Block (SGB), where an anesthetic is placed at C-6 level and a more refined version of CSB, where combination of C6 and C4 block is performed, are both medically-based treatments for PTSD. SGB was the original sympathetic block, but a combination of C6 and C4 block seems to provide greater efficacy due to action in different parts of the brain [11]. CSB is of potentially great significance for those suffering from the disorder, including those who have failed conventional therapies [11]. The rapid response and destigmatization of the procedure may enable this technique to be beneficial for patient populations which are particularly difficult to treat, including military service members and veterans [11]. Dr. Olmsted et al. demonstrated in a 2019 RCT that active injectate on the right side was twice as effective as placebo for 8 weeks [12]. A prior 2016 RCT by Dr Hanling et al. found no appreciable difference between SGB and sham treatment on psychological or pain outcomes [13]. During a review of above by the VA it was determined that the study was imprecise, with moderate methodological limitations. Researchers did not use the most common administration techniques, concluding that the study provides an insufficient basis upon which to draw conclusions about the efficacy of SGB in the treatment of PTSD in Veterans [14].

It is likely that the mechanism involves modulation of nerve growth factor (NGF) and reduction of norepinephrine (NE) [15]. SGB has been shown to improve memory function in PTSD patients [16], as well as prevent pathological damage of the hippocampus while maintaining spatial learning and memory function in a sleep-deprived rat model. This occurs due to reduced expression of IL-6, IL-1β and Caspase-3 in the hippocampus [17]. Dr. Yang showed that SGB could result in significant reduction of serum inflammatory cytokines IL-6, IL-1β and TNF-α in TBI patients. SGB could alter the post-TBI nerve-endocrine-immune system dysfunction. This may lead to improved cerebral circulation and improved clinical outcomes [18].

It is likely that an alarming increase in the incidence of suicide in the SOF community is due to limited effective treatments for this unique and complex population [1]. Given the comorbid presentations associated with PTSD (depression, anxiety, TBI), there is a great need to develop effective treatments that can simultaneously address PTSD and associated comorbidities [19].

2. Methods

2.1. Cervical sympathetic block (CSB)

Detailed informed consent was obtained prior to all procedures for CSB. The patient was placed in the supine position with the head rotated slightly to the left, with monitoring per clinic protocol. The skin of the neck was cleaned with chlorhexidine-isopropyl alcohol preparation and 2 g of sterile ultrasound gel was applied. The neck was scanned using a broadband linear transducer (8–13 from the level of the 6th to the 4th cervical vertebrae in transverse view). The skin at the injection site on the lateral neck was anesthetized with 1.5 mL of 1% lidocaine. Utilizing an in-plane approach, under real-time ultrasound guidance, a 22-gauge echogenic needle was placed just dorsal to the ventral fascia of the longus coli, medial to the longus capitus. After attempted aspiration, while monitoring the patient, 0.5 mL of 0.5% bupivacaine was injected, and after observing the patient for 30 s, a second 4 mL aliquot was injected. The patient was monitored for an additional 30 s. After the patient verbally confirmed an absence of any concerning symptoms, an additional 4 mL of 0.5% bupivacaine was slowly injected over 1 min for a total injection volume of 8 mL for a single-level block. This was repeated at the 4th cervical level, with a total of 4 mL of bupivacaine. Left-sided CSB was performed the following day due to possible safety considerations.

2.2. Ketamine infusion (KI)

Detailed informed consent was obtained prior to all infusions following a consultation. The initial infusion of racemic ketamine hydrochloride (0.5 mg/kg) was administered over 45 min. Premedication with ondansetron 4 mg IVP was used for all sessions and an anesthesiologist was present until discharge. During the infusion, a nurse recorded vital signs (heart rate, blood pressure, respirations, pulse oximetry) and clinical status every 5 min. Any concerning or intolerable treatment-emergent side effects (e.g., hemodynamic

instability, severe dissociation, worsening depression or anxiety) prompted intervention or discontinuation of the infusion. At the end of each infusion, the patient was clinically monitored for at least 1 h by the nursing staff. Subsequent infusions utilized escalating doses of ketamine of 0.1–0.2 mg/kg titrated to induce mild to moderate dissociation. (See Fig. 1 for detailed timing of ketamine administration, dose report and timing of CSB.) A total of 5 KI were performed.

2.3. Outcome measures

The PTSD Checklist for DSM-V (PCL-5) is a 20-item self-reported questionnaire that assesses PTSD symptomatology based on 20 symptoms outlined in the DSM-5. The purposes of this test include screening, diagnosis, and monitoring of symptomatology over a period of time. The patient is to self-report a score based on a 5-item Likert scale from 0 to 4, which is described by the following: 0) "Not at all"; 1) "A little bit"; 2) "Moderately"; 3) "Quite a bit"; and 4) "Extremely". It should be noted that there are a number of differences between PCL-5 and PCL-4 (based on DSM-IV), hence they can neither be compared nor interchanged. The total symptom severity is a sum of the patient responses and may range from 0 to 80. A change in PCL-5 score by 5–10 points is considered reliable, and by 10–20 points is considered clinically significant. The optimally efficient minimum cutoff score that is considered diagnostic ranges from 31 to 33 [20].

The Beck Depression Inventory (BDI) is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of depression for the purpose of evaluating symptom severity [21]. The patient is to self-report a score based on a 4-item Likert scale from 0 to 3, which is described by the following: 0) "Symptom Absent"; and 4) "Severe Symptoms Present". Score interpretation is dependent on a previous diagnosis of depression. A score greater than 20 without a previous diagnosis indicates depression. If a diagnosis of depression has already been made, the following score ranges can indicate the severity of symptoms: 0–13 = minimal depression; 14–19 = mild depression; 20–28 = moderate depression; and 29–63 = severe depression [22].

The Beck Anxiety Inventory (BAI) is a 21-item, self-report rating inventory that measures characteristic attitudes and symptoms of anxiety for the purpose of evaluating symptom severity. BAI is based on four factors of anxiety: subjective, neurophysiological, autonomic, and panic. The patient is to self-report a score based on a 4-item Likert scale from 0 to 3, which is described by the following: 0) "Symptom Absent"; and 4) "Severe Symptoms Present". Total score ranges from 0 to 63, and there are different established score cut off minimums for different diagnoses: 8 – panic disorder; 3.5 – phobia, generalized anxiety disorder. It should be noted that total BAI score can accurately indicate that an individual has panic disorder, but not any other anxiety disorder [23]. This confirms a previous finding that BAI is a quantitative measure of panic symptoms rather anxiety in general [24].

The Concise Health Risk Tracking Self Report (CHRT) is a 14-item, self-report questionnaire that assesses suicidal ideation and thoughts that may indicate the inclination for suicidal action, interpreted in terms of propensity, impulsivity, and risk of suicide. The questions are in regard to hopelessness, self-worth, pessimism about the future, perception of social support, and active suicidal planning [25]. The patient is to self-report a score based on a 5-item Likert scale from 0 to 4, which is described by the following: 0) "Strongly Disagree"; and 4) "Strongly Agree". Total score ranges from 0 to 56. Propensity is calculated by summing the scores of questions 1–9, and pertains to feelings of pessimism, helplessness, despair, and level of social support. Impulsivity is calculated by summing the scores of questions 10–11 and pertains to acting or speaking without prior thought. Risk of suicide is calculated by summing questions 12–14, and pertains directly to having thoughts of suicide, ideas of possible ways to commit suicide, and having a specific plan to commit suicide [25].

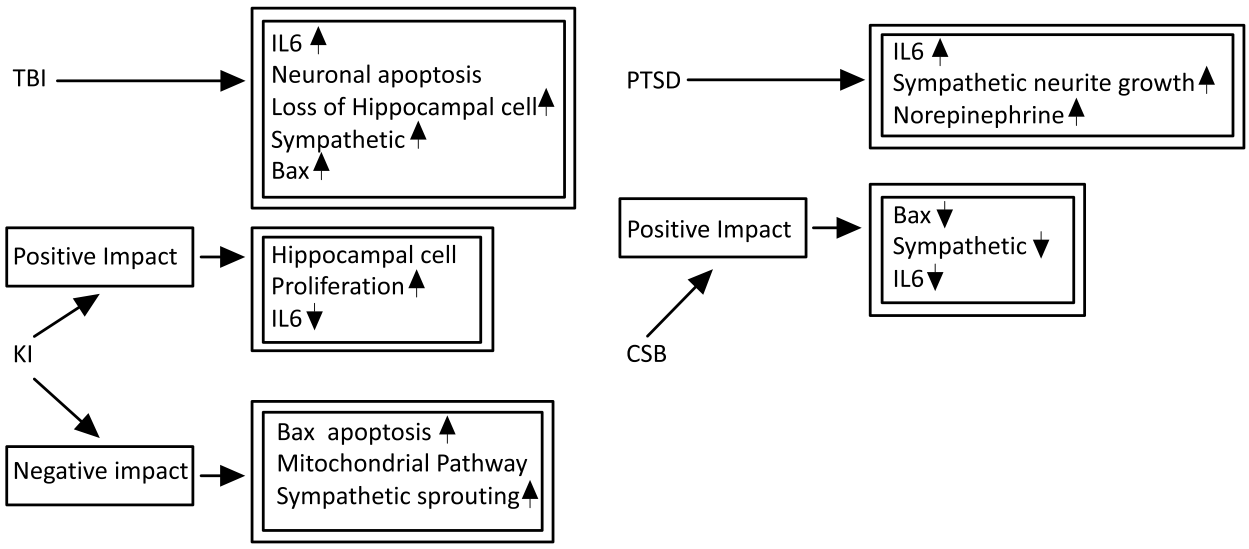

Fig. 1. Summary of neurobiologic changes due to TBI and PTSD as well as the impact of KI and CSB. Traumatic Brain Injury (TBI), Post Traumatic Stress Disorder (PTSD) , Ketamine (KI), Cervical Sympathetic Block (CSB).

3. Case report

The patient was a 40-year-old male. He completed five combat deployments to Afghanistan between 2004 and 2014, with a total time deployed of 37 months. During all the deployments, he was exposed to dead bodies, explosions, constant danger, and the killing of humans and animals. His career started as an infantryman during his 2004–2005 deployment, and the rest of the time he served in Special Forces. The patient also had significant history of childhood sexual and physical abuse that occurred during 1988–1996 (age 8 to 16) from his stepfather, with over 100 encounters during the eight years of abuse. The patient had a history of ethyl alcohol dependence from 1999 to 2019, at which point he was diagnosed with alcohol abuse disorder, characterized by binge drinking 10–12 drinks per day on weekends. He was also addicted to tramadol and oxycodone between 2011 and 2014, and to intravenous Nubain (nalbuphine hydrochloride, a synthetic opioid) between 2012 and 2014. He suffered emotional trauma from the loss of multiple friends to suicide and war, and moral injuries sustained during his deployments. He attempted suicide in 1992, 2016 and 2019.

The patient started psychotherapy in 1996 and completed EMDR therapy in three months, seeking help with sexual trauma, but this method was extremely painful. Those three months cost $100,000 and provided only 50% relief. The patient had three admittances to psychological wards, for depression, PTSD and TBI. He learned many life skills in the rehab clinic that he still uses today. The patient recalls being placed on Prozac and Wellbutrin, however, at the time of KI and CSB injection the patient was medication-free. He had misdiagnosed with bipolar disorder in 2019, for which he took medication for approximately four months before treatment cessation. TBI was brought up as a diagnosis as an inpatient at Emerald Coast Behavioral Hospital in Panama City Beach, Florida in September 2019. He completed a 90 day multipath rehab inpatient course. The official diagnosis was made with an MRI in June 2021, where white matter change was noted at Fort Bragg Clinic, NC. He reported having a hard time concentrating on multiple tasks and keeping his mind present, as per a prior intervention report. The patient reported experiencing impulsivity and disordered sleep. His mind was always in another place, replaying memories of the past. In his words, "This extra mind use to maintain focus on tasks became very exhausting on mind and body". The patient received 5 KI and SGB to the left and ride sides in Chicago, in July 2021. He had been sober for two years at this point. The patient was diagnosed with PTSD at the VA and Emerald Coast Behavioral Hospital, by a military psychiatrist. Considering the marked and prolonged trauma experienced, he likely fulfills the criteria of complex PTSD, which is a form of PTSD characterized by prolonged or repetitive exposure to a series of traumatic events, in which the individual perceives little or no chance of escape [26].

3.1. Post treatment self-report

CSB and KI have been the most impactful interventions in his day-to-day life. He is now present and able to complete work without the invasive memories of the past. Childhood memories and traumatic events through the deployments seem as if they are long ago memories. The memories of the past seem as if they have faded away and do not hurt anymore. Low moods are no longer a constant for him, neither are depressive symptoms prominent in his life.

Compared to the patient's baseline, his psychiatric profile at the one year follow-up showed sharp improvements, with reductions of 93.55% in his depression score (from severe (31/63) to mild depression (2/63)), of 86.67% in anxiety (from mild (15/63) to minimal anxiety (2/63)), of 73.81% in PTSD symptoms (from probable PTSD (42/80) to not meeting criteria for PTSD (11/80)), of 75% in suicidality (from 8/12 to 2/12), and of 100% in impulsivity (from 6/8 to 0/8). For more details, see Table 1.

4. Discussion

As discussed above, soldiers from the SOF community are likely to present with a PTSD/TBI mixed presentation. It seems likely that TBI and PTSD can be produced by overlapping pathophysiological changes that disrupt neural connections, termed the "connectome" [27]. The neural disruptions shared by PTSD and TBI, as well as the comorbid conditions, include asymmetrical white matter tract abnormalities and gray matter changes in the basolateral amygdala, hippocampus, and prefrontal cortex. These disturbances produce neuronal death and degeneration, axonal injury, and dendritic spine dysregulation and changes [27].

TBI induces a multifaceted range of immunological and inflammatory tissue responses with similarities to ischemia and reperfusion injury. Neuronal apoptosis is the main characteristic of secondary brain injury, and in the human hippocampus, neuronal cell death is

Table 1
Detailed summary of pre treatment measures and follow up measures on day 394.

Day	0	1	2	3	4	5	394	% Reduction	Point Reduction
Procedure(s)	KI	KI	Right CSB	Left CSB + KI	KI	KI			
BDI (Depression)	31				3		2	93.55	29
BAI (Anxiety)	15				1		2	86.67	13
PCL-5 (PTSD)	42						11	73.81	31
CHRT (Propensity)	21	11		12	4		2	90.48	19
CHRT (Impulsivity)	6	3		5	4		0	100.00	6
CHRT (Suicidality)	8	6		4	0		2	75.00	6
CHRT (Total)	35	20	0	21	8	0	4	88.57	31
KI dose (mg)	52	65		75	90	100			

evident up to 1 year after TBI [28] To underscore the above, the finding of Interleukin-6 (IL-6) increased in TBI [29] Kumar and corresponding CSF IL-6 levels increased in PTSD patients are consistent [30]. TBI can induce expression of the apoptotic protein bcl-2-like protein 4 (BAX) [31]. Additionally, stress exposure can persistently upregulate brain expression of BAX in a zebrafish model [32]. Furthermore, TBI is correlated with an exaggerated stress response due to plasma catecholamine levels, known as sympathetic storming. It is also known as autonomic dysfunction syndrome, as autonomic balance dysregulation results from loss of cortical control due to the brain injury [33]. One explanation for the development of PTSD is an acute increase in NGF and mediated growth of sympathetic neurites, eventually leading to an increase in brain NE and ensuing symptoms of PTSD [15].

The mechanisms of the combined effect of KI and SGB are not well understood. To the best of our knowledge, this is the first publication of combined techniques to treat PTSD/TBI symptoms. Several findings point to possible reasons for a synergistic impact of this new protocol. KI can produce changes that are associated with improvement in neurogenesis-related behavioral recall tasks, suggesting a possible benefit from ketamine administration following TBI in mice [8]. Similar findings have been shown by Browne, who found that ketamine may be effective for treating neuropsychiatric complications that emerge following mild single-blast overpressure (mbTBI), which is a common type of injury in SOF [9].

4.1. KI and PTSD

Dr. Liriano reported a near complete resolution of PTSD symptoms over the short term and seemed to have similar findings regarding the use of ketamine in major depression. It is thought that upregulating BDNF and antagonizing NMDA serve to reverse some of the damage caused by chronic stress [10]. Yet ketamine can induce toxicity in human neurons through reactive oxygen species-mediated activation of the mitochondrial apoptotic pathway and autophagy. “Results showed that ketamine induced apoptosis through activation of the mitochondrial pathway by increasing the expression of BAX, while simultaneously decreasing the expression of Bcl-2 (BAX antagonist) at the protein level” [34]. Further, chronic treatment with ketamine caused significant ventricular myocardial apoptosis, fibrosis, and sympathetic sprouting, which altered the electrophysiological properties of the heart and increased its susceptibility to malignant arrhythmia that may lead to sudden cardiac death [35].

The finding of interest is that SGB can reduce the apoptosis of neurons in rats and improve brain injury by inhibiting the expression of the pro-apoptotic protein BAX [36]. SGB can prevent pathological damage of the hippocampus and maintain spatial learning and memory function in a sleep deprived rat model. This occurs due to reduced expression of IL-6, IL-1β and Caspase-3 in the hippocampus [17]. SGB can reverse sympathetic sprouting [15] by reducing NGF regulated neurite growth [15], thus opposing the effect of KI. This is partly responsible for the rapid and persistent reduction of the PTSD symptoms known to be related to heightened norepinephrine levels [15]. SGB is thought to reduce concentration of NGF and NR while inducing sympathetic pruning, which is the removal of extra sympathetic neurite growth, leading to a reduction of PTSD symptoms [15]. See Fig. 1 for a summary of proposed mechanisms.

4.2. Limitations

The main limitation of this report is the one patient included for the prolonged follow-up, thus generalization to others should be limited. Further, isolating the independent effects of KI and CSB, from the synergetic KI and CSB effect is difficult and would require a large, multi-arm preferably multicenter study. Yet, considering the acute need for treatment of suicides and other PTSD symptoms in SOF personnel combined with a possible biologic explanation available, the combined KI and CST impact on clinical symptoms should be evaluated in the near future.

5. Conclusion

As demonstrated above by the case study, combined KI and CSB appear to have a profound and long lasting (over 1 year) impact on the symptoms of TBI and PTSD. Although the mechanisms of the effect are not fully elucidated, it provide a very effective new treatment for this unique and complex population. Further study is need to determine the true promise of this combined KI/CSB technique.

Declarations

Prior presentations

None.

Clinical trial registration

Not applicable.

Institutional animal care and use Committee (IACUC)

Not applicable.

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Competing interests

None.

Individual author contribution statement

EL performed sympathetic blocks, analyzed the data and drafted the original manuscript. ZS and GN collected the data and edited the manuscript. ZS produced the table and figure. CF reviewed and edited the final version of the manuscript. All authors read and approved the final manuscript.

Data availability statement

Not applicable.

Disclaimer

None.

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