ORIGINAL ARTICLE

5-HYDROXITRYPTOPHAN DIETARY SUPPLEMENTATION IN POST-TRAUMATIC STRESS SYNDROME

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Abstract

Major depressive disorder (MDD) is a common psychological long-term consequence of patients that have been treated in intensive care units together with anxiety disorders (AD) and posttraumatic stress disorder (PTSD). This study aimed to investigate the effect of 5-hydroxytryptophan administration on serotonin levels in critically ill patients and the prevalence of psychiatric disorders in our patients. A randomized controlled trial was conducted in the Anaesthesia and Intensive Care Unit, Clinical Emergency Hospital Bucharest, Romania, on patients admitted for severe non-surgical illness aged from 18 to 55 years. Thirty subjects were recruited and randomized through sealed envelopes with a concealed 1:1 allocation to either treated or control group: Group 1 - placebo (control group) and Group 2 (5-TRP group) - treated with 300 mg of 5-hydroxytryptophan twice daily. After 7 days, Group 2 had higher levels of serum serotonin (230.06 ± 34.96 µg/L) in comparison to the control group (181.20 ± 38.87 µg/L; $p < 0.001$). The incidence of depression was 24.49% in Group 2 and 42.17% in Group 1 ($p < 0.005$) after 30 days of observation. Our results suggest that due to his role as an immediate precursor, 5-hydroxytryptophan increases the plasma level of serotonin, with a beneficial effect on anxiety and depression of the treated patients.

Rezumat

Tulburarea depresivă majoră (MDD) este o consecință psihologică frecventă pe termen lung a pacienților care au necesitat suport vital în unitățile de terapie intensivă însoțită frecvent de tulburări de anxietate și de tulburarea de stres posttraumatic (PTSD). Studiul de față și-a propus să investigheze efectul administrării de 5-hidroxitriptofan asupra nivelului serotoninei la pacienții în stare critică precum și prevalența tulburărilor psihice la pacienții înrolați. Am realizat un studiu controlat randomizat în cadrul Secției de Anestezie și Terapie Intensivă-Toxicologie, Spitalul Clinic de Urgență București, România cu înrolarea pacienților admiși pentru afecțiuni severe non-chirurgicale, având vârsta cuprinsă între 18 și 55 de ani. Treizeci de participanți au fost recrutați și randomizați prin plicuri sigilate cu o alocare ascunsă 1: 1 fie la grupul tratat, fie la grupul de control: Grupul 1 - placebo (grupul de control) și Grupul 2 (grupul 5-TRP) - tratat cu 300 mg de 5-hidroxitriptofan de două ori zilnic. După 7 zile, grupul 2 a avut niveluri serice de serotonină mai mari ($230,06 \pm 34,96$ µg/L) comparativ cu grupul martor ($181,20 \pm 38,87$ µg/L; $p < 0,001$). Incidența depresiei a fost de 24,49% în grupul 2 și de 42,17% în grupul 1 ($p < 0,005$) după 30 de zile de observație. Rezultatele noastre sugerează faptul că, datorită rolului său de precursor imediat, 5-hidroxitriptofanul crește nivelul plasmatic al serotoninei, cu efect benefic asupra anxietății și depresiei pacienților tratați.

Keywords: L-tryptophan, serotonin, depression, anxiety

Introduction

Mortality related to critical illness has been decreasing over the past years, but the number of patients with long-term functional disabilities after Intensive Care Units (ICU) admission has increased and lead to various healthcare issues. Psychiatric diseases represent a large spectrum of ICU admission related problems, major depressive disorder (MDD) being the most common, along with anxiety disorders (AD) and posttraumatic stress disorder (PTSD). A holistic approach (music therapy, massage, reflexology, relaxation, clinical psychology sessions and nutrition therapies) appears to have positive results for this category of patients [1-3].

The most relevant criteria for ICU patients' prognosis are considered the initial health status, highlighted during the pandemic. Other aspects like duration of mechanical ventilation/ICU stay/sedation, the severity of medical illness, age, or gender were found to be relevant in this context [4-6].

The prevalence of PTSD among ICU survivors, according to Nikayin *et al.*, was estimated from 4 to 62% and symptoms of anxiety following critical illness occur in 25 - 46% of patients after ICU discharge in a period ranging from 3 to 14 months, being more common in women aged from 30 to 44 years. The same author found that around 29% of Intensive Care Unit (ICU) survivors develop depressive symptoms over the years'

post-discharge, and those are associated with signs of psychological distress (anxiety, stress and anger) [7]. An increased risk of suicide and self-harm was found in this category of patients and evaluated as 3.4 times higher than the general population over a 5 years period the following discharge [5].

Although the aetiology is unclear, one of the pathogenic processes involved appears to be correlated with neuro-transmitters alteration in the central nervous system; namely, central serotonin levels were decreased in ICU survivors [8, 9].

Tryptophan is an essential amino acid that acts as a precursor for several bioactive compounds, including nicotinamide (vitamin B$_3$), serotonin, melatonin, tryptamine, kynurenine, 3-hydroxykynurenine, and quinolinic and xanthurenic acids. Only a reduced fraction of the 5-hydroxytryptophan administered is transformed into serotonin, up to 95% taking the kynurenine pathway (KP) [10, 11]. In the past few years, several studies have described the role of the tryptophan-kynurenine system in physical activities, inflammation, and mental health [12-14]. Moreover, pandemic restrictions altered the dietary patterns of the general population [15].

In order to mitigate these problems, a multimodal intervention is needed, and nutrition therapy should be administrated during ICU admission and after hospital discharge [3, 16].

Targeting the serotoninergic system dysfunction as a substrate for psychiatric disorders like MDD, AD and PTSD, we analysed the correlation between the administration of 5-hydroxytryptophan, serotonin plasma levels and the clinical evolution of the studied ICU patients.

Materials and Methods

Subjects

This was a randomized controlled trial conducted in the Anaesthesia and Intensive Care Unit of the Clinical Emergency Hospital Bucharest, Romania that included all patients admitted for severe non-surgical illness, aged from 18 to 55 years. We excluded all subjects suffering from liver or kidney conditions and patients having previous neurologic or mental disorders and an American Society of Anaesthesiologists score (ASA) lower than 3 [17]. The study was approved by the Hospital Ethics Committee and was conducted in accordance with the Declaration of Helsinki.

Procedures

Thirty participants were recruited and randomized through sealed envelopes with a concealed 1:1 allocation to either the intervention or control group according to depression prevention: Group 1 did not receive any treatment and Group 2 received the dietary supplementation as 300 mg of 5-OH-tryptophan twice daily. Study drug administration was continued for 30 days regardless if the patients were discharged or not from the ICU. The initial dose of the study drug was administered at the admission time.

Data and Measurement

Baseline admission assessment included depressed mood measured by the two-question depression screen [18], e.g. Post-Traumatic Stress Symptoms Checklist-10 (PTSS-10) and Hospital Anxiety and Depression Scale (HADS), co-morbidity burden by the Charlson Index and American Society of Anaesthesiologists (ASA) score. We recorded all variables regarding cardiac, pulmonary, renal, neurologic, and infectious complications as well as sepsis and thrombotic events. In order to assess serotonin levels, blood samples were obtained during the admission procedure, collected following standard guidelines, and plasma was separated and stored at -20°C until used to analyse serotonin levels, using HPLC on an Agilent 1260. Cut-off values for serotonin were considered to be 80 - 400 μg/L, and the detection limit was 5 μg/L. Plasma levels of serotonin were repeated after 7, 14 and 30 days of treatment.

The Post-Traumatic Stress Symptoms Checklist-10 (PTSS-10) was used to evaluate the symptoms of anxiety and depression, on admission and after 30 days. This assessment is a validated screening tool for the detection of PTSD-related symptoms among ICU surviving patients. The first part of the test (Part A) contains four questions regarding memories of traumatic events and feelings while in the ICU, such as night-mares, anxiety or panic, pain or trouble to breathe. The answer is either yes or no. The second part (Part B) is detailed upon 10 questions focused on stress symptoms. The total score is expressed from 10 to 70 points, obtained from every item scored from 1 (never) to 7 (always). As demonstrated previously, a score above 34 in PTSS-10 part B indicates clinically significant posttraumatic stress symptoms and is associated with a diagnosis of PTSD.

Statistical analysis

Statistical analysis was performed on Statistical Package for Social Sciences (SPSS) version 18.0 using Shapiro-Wilk, Chi-square, Mann-Whitney U-test and binomial logistic regression test. Fisher's exact test was used to compare treatment groups in the analysis of categorical variables (e.g., gender). The differences in serum profiles were determined by an analysis of covariance. Statistical significance was set for a p-value less than 0.05.

Results and Discussion

A number of 42 patients were initially enrolled, but the final study population consisted of 30 patients due to incomplete data collection or patients withdrawn from the study. The subjects' ages ranged between 19 and 57 years, with a mean of 50.03 ± 13.13 years, with no differences between the two study groups: 51.06 ± 11.73 and 49.00 ± 14.74 years for Group 1 and Group 2, respectively.

	Group 1 (n = 15)	Group 2 (n = 15)	p
Age (years)	51.06 ± 11.73	49.00 ± 14.74	n/s
Male (%)	13.33	13.33	n/s
Comorbidities (Charlson Index)	2.8 ± 1.8	2.9 ± 2.1	n/s
Creatinine (mg/dL)	1.5 ± 0.3	1.3 ± 0.3	n/s
Albumin (gm/dL)	4.8 ± 0.5	4.7 ± 0.5	n/s
Haematocrit (%)	47 ± 6	48 ± 3	n/s
Sodium (mEq/L)	137 ± 3	140 ± 3	n/s
Potassium (mEq/L)	4.2 ± 0.3	4.3 ± 0.4	n/s
ASA Score (≥ 3)	81%	85%	n/s
Serotonin (µg/L)	113.00 ± 49.66	122.53 ± 28.73	n/s

ASA = American Society of Anaesthesiologists score, n/s = p > 0.05

Baseline characteristics
The admission baseline characteristics are presented in Table I. No significant differences were found between the two groups, including serotonin levels.
Serotonin levels
After 7 days, Group 2 had higher levels of serum serotonin (230.06 ± 34.96 µg/L) compared to Group 1 (181.20 ± 38.87 µg/L; $p < 0.001$) (Figure 1).
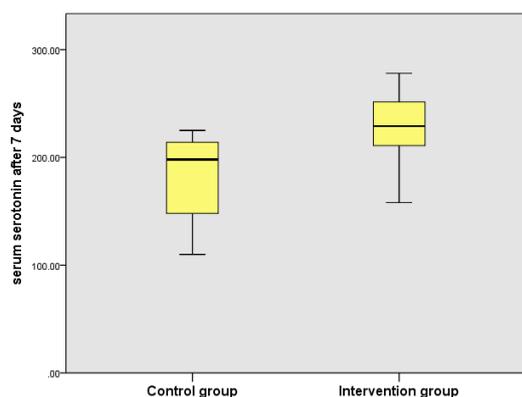

Figure 1.
Serum serotonin level after 7 days

After 14 days of treatment, serum level of serotonin was also higher in the Group 2 when compared to control (211.80 ± 52.58 µg/L *vs*. 163.26 ± 37.72 µg/L, $p < 0.05$) (Figure 2).
The final serotonin evaluation after 30 days of treatment revealed statistical significance (221.89 ± 59.28 µg/L

vs. 173.46 ± 34.27 µg/L, $p < 0.05$). Acute tryptophan depletion is correlated with anxiety disorders [7].
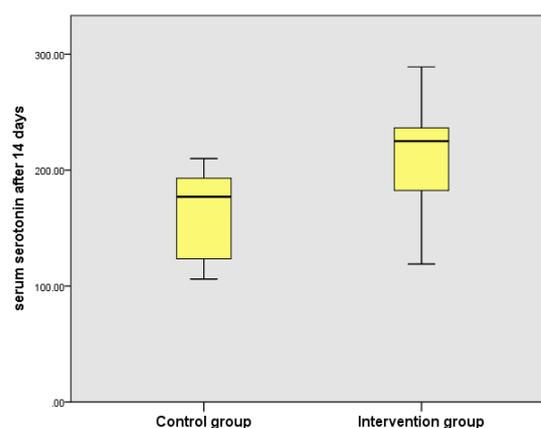

Figure 2.
Serum serotonin level after 14 days

PTSS-10 score
On admission, there was no difference regarding mean PTSS-10 in the study population (38.43 ± 4.67 *vs*. 37.72 ± 6.45, in the Group 2 and Group 1, respectively). By the end of the study, in the 30th day of treatment, Group 1 had higher psychological score than Group 2, indicating a more likely possibility of developing PTSS (35.13 ± 7.56 *vs*. 28 ± 4.01). The difference in mean score between groups was also statistically significant ($p = 0.003$) (Table II).

Table II
PTSS-10 and HADS scores among the studied population

	Group 1 (n = 15)	Group 2 (n = 15)	p-value
PTSS-10			
Admission	37.72 ± 6.45	38.43 ± 4.67	0.812
After 30 days	28 ± 4.01	35.13 ± 7.56	0.003
HADS			
Admission	12.5 ± 5.66	13.8 ± 6.33	0.563
After 30 days	11.3 ± 5.67	10.4 ± 4.33	0.004

PTSS-10: Post-Traumatic Stress Symptoms Checklist-10, HADS: Hospital Anxiety and Depression Scale

The same method using clinical predictive score values was used in previous psychiatric pathology studies. The incidence of depression was 24.49% in Group 2 and 42.17% in Group 1 (p < 0.005). A part of the clinical effect might be explained by the importance of serotonin receptors' activity in pain therapy, considering that pain has a triggering role in PTSS incidence (Table II).

Plasmatic concentrations of serotonin are correlated with central serotonin levels, depletion of the tryptophan in the nervous system being triggered by acute tryptophan depletion (ATD) in the plasma, a phenomenon widely described even in healthy patients [19-21].

Thus, for optimal levels of serotonin in the brain, oral supplementation with 5-hydroxytryptophan can be a sustainable approach [22], although there might be other metabolites and exogenous substances that interact with mental status [23].

Serotonin continues to be one of the most active neurotransmitters, neurohormones and blood factors, controlling the central and peripheral functions. Due to its significant role, the serotoninergic system is subjected to several therapeutic classes such as selective serotonin reuptake inhibitors, triptans, antiemetic, analgesic agents or appetite suppressants. Serotoninergic system activity varies in population, with some individuals having increased serotonin activity, which may lead to a series of health issues described as serotonin syndrome when associated with serotoninergic agents. Five-hydroxytryptophan orally administered follows a specific metabolic pathway generating serotonin after decarboxylation under the enzyme aromatic-L-amino-acid decarboxylase activity with the help of vitamin B_6 [22]. This reaction occurs in both the liver and nervous tissues, with a reduced fraction of the initial dose converting to serotonin, up to 95% taking the kynurenine pathway [10, 11]. Still, as an endogenous molecule, serotonin has an intense biological activity. Otherwise, kynurenines have particular roles in inflammation, immune response and muscular movement [12].

In our study, the serotonin input and the kynurenine modulation induced after 5-hydroxytryptophan administration [24] appears to have a synergic effect on preventing mental health issues related to ICU admission.

Differences between Group 2 and Group 1 have statistical significance, at the end of the observation period, revealing the benefits of dietary supplementation with 5-hydroxytryptophan. Higher plasmatic concentration of serotonin and reduced incidence of mental health issues have been reported during this study. These outcomes are based on tryptophan's biological pathways, which lead to serotonin, melatonin, another bioactive compound that improves memory function and cognitive process [25, 26].

The results obtained in this study pointed out the importance of dietary supplementation as a current therapeutic approach in modern risk stratification to several health issues, such as mental health diseases [27, 28], diabetes mellitus [29, 30], and cardiovascular insufficiency [31, 32] or fungal infections [33, 34]. This type of dietary intervention appears to be an available approach to the cost associated with prevention, aiming to optimal therapeutic outcomes [35].

Conclusions

The results of the study pointed out a functional correlation between oral supplementation of 5-hydroxytryptophan and plasma levels of serotonin with possible beneficial results for critically ill patient evolution after ICU discharge. Further investigations should be conducted to define 5-hydroxytryptophan as a prophylactic agent for a range of psychiatric disorders such as MDD and PTSD.

Conflict of interest

The authors declare no conflict of interest.

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