Evaluation the effects of Pycnogenol (French maritime pine bark extract) supplementation on the inflammatory biomarkers, nutritional and clinical status in traumatic brain injury patients, in Intensive Care Unit; A Randomized Clinical Trial protocol

Mahsa Malekahmadi
Mashhad University of Medical Sciences https://orcid.org/0000-0002-6707-6929
Omid Moradi Moghaddam
Iran University of Medical Sciences
Mohsen Nematy
Mashhad University of Medical Sciences
Safieh Firouzi
Mashhad University of Medical Sciences
Abdolreza Norouzy (norouzya@mums.ac.ir)

Study protocol

Keywords: Traumatic brain injury; critical care; pycnogenol; inflammation; nutrition support.

Posted Date: July 19th, 2019

DOI: https://doi.org/10.21203/rs.2.11720/v1

Version of Record: A version of this preprint was published on February 11th, 2020. See the published version at https://doi.org/10.1186/s13063-019-4008-x.

Abstract

Background Traumatic brain injury (TBI) is one of the major health and socioeconomic problems in the world. Immune-enhancing enteral formula has been proven to significantly reduce infection rate in TBI patient. One of the ingredients that can be used in immunonutrition formulas to reduce inflammation and oxidative stress is pycnogenol. Objective surveying the effect of pycnogenol on the clinical, nutritional and inflammatory status of TBI patients. Methods This is double-blind, randomized controlled trial. Block randomization are used. Intervention group will receive pycnogenol supplement 150 mg for 10 days. Control group will receive placebo for the same duration. Inflammatory status (IL-6, IL- 1β, C-reactive protein, IL-10) and oxidative stress status (Malondialdehyde, total antioxidant capacity), at the base line, at the 5th day and at the end of the study (10th day) are measured. Clinical and nutritional status will be assessed three times during the intervention. SOFA (sequential organ failure assessment) questionnaire for assessment of organ failure filled out every other day. The mortality rate will be asked within 28 days of the start of the intervention. Weight, body mass index and body composition are measured. All analyses will be conducted by initially assigned study arm in an intention-to-treat analysis. Discussion we will expect supplementation of 150 mg pycnogenol improves clinical and nutritional status of the TBI patients and reduces inflammation and oxidative stress in the 10 days of intervention.

Background

Traumatic brain injury

Traumatic brain injury (TBI) is one of the major health and socioeconomic problems in the world (1). It is prevalent in both developed and developing societies and affects people of all ages. TBI is called the ‘silent epidemic’ because problems resulting from TBI don’t occur immediately (2).

TBI causes about 1.5 million deaths and hospitalizations per year in the USA (3). TBI is more common among teens and young adult aged 15-45 years, mainly due to road accidents and sport-related events. Men are three times more likely to be injured and more severely damaged (4).
“Traumatic brain injury” is used instead of ‘head injury’ because it better shows the importance of the ‘brain’ (5). TBI is defined as: ‘An alteration in brain function or physiology due to external force or shock from the outside (6).

Patients on the basis of Glasgow Coma Scale are categorized into three groups: mild, moderate, and severe. Glasgow Coma Scale (GCS) is a system used to assess coma and impaired consciousness (7). A GCS score of 13–15 is defined as mild, 9–12 as moderate, and 3–8 as severe (7).

The mechanisms of damage to the brain tissue associated with TBI is classified into two primary and secondary categories. Primary damage due to the mechanical force involved in the skull and the brain, which seems to be irreversible (8). The primary injury complications include: brain contusions, axonal injuries, rupturing of blood vessels, and intracranial hemorrhages. Secondary injury complications progress over time (9). The secondary injury complications include: elevated intracranial pressure, blood-

brain barrier (BBB) disruption, neuroinflammation, brain edema, cerebral hypoxia, ischemia, and delayed neurodegeneration (10-12)

Neuroinflammation in TBI

Cytokines, chemokines, and growth factors have proven to play important roles in the pathophysiology of TBI. Immediately after brain injury, Proinflammatory cytokines, such as IL-1β, IL-6 and tumor necrosis factor-α (TNF-α) as well as transforming growth factor-beta (TGF-β) are produced in large volume. These worsen the condition of trauma and delay the recovery by producing oxidative stress and Matrix metalloproteinases (MMPs) (13, 14). These post-traumatic inflammatory cascades cause blood brain barrier (BBB) dysfunction, which ultimately leads to the influx of inflammatory cells from the blood to the brain (15).

Production of reactive oxygen substrates (ROS) directly or indirectly, as oxidative by-products of lipids, proteins, or nucleic acids are common following traumatic brain injury. Malondialdehyde (MDA) are the major by-products of lipid peroxidation. MDA is potentially atherogenic lipid peroxide and generated in vivo via peroxidation of polyunsaturated fatty acids (16).

Nutrition support in TBI

Nutritional support is an important issue in intensive care for critically ill patients such as traumatic brain injury patients. Patients with TBI often are in a hypermetabolic state, the energy expenditure is increased (17).

Early nutrition support in TBI patients result in a significant reduction in mortality rate, less infectious complications and lower risk of poor outcome (18).

There has been growing use of immunonutrition to modulate the inflammatory response in injury or infection and to improve clinical outcome (19). immune-modulation enteral formula has been proven to significantly reduce infection rate in TBI patients (20). One of the ingredients that can be used in immunonutrition formula to reduce inflammation and oxidative stress is pycnogenol.

Pycnogenol

Pycnogenol® (PYC), recognized as one of the most powerful natural antioxidants, is a bark extract of the French maritime pine (*Pinus pinaster*), and is rich in flavonoids. Main component of PYC are polyphenols, specifically mono- and oligomeric units of caffeic acid, ferulic acid, catechin, epicatechin, and taxifolin (21). it is classified as GRAS (generally recognized as safe) in the USA (22). Clinical effects of pycnogenol include: endothelium-dependent vasodilator activity (23), and anti-thrombotic effect as shown by numerous in vitro and in vivo investigations in animals and human clinical research studies (24, 25).

PYC prevents neurotoxicity and apoptotic cell death in oxidative stress status (26, 27). Also, PYC protects against lipid peroxidation, and pro-oxidants and peroxynitrites (28, 29). And the animal studies proved the protective effect of PYC following traumatic brain injury by suppressing of IL-6 and TNF-α level (30, 31).

No serious adverse effect has been seen in any clinical trials or commercial use (32). The most commonly observed adverse effect is gastric discomfort due to mild and transient nature, and did not report when consumed with or after meals (22).

Methods

Patient selection

Inclusion criteria

All TBI patients admitted directly or transferred to the intensive care units of participating hospital are evaluated for eligibility for entry into the randomized clinical trial. Preliminary eligibility criteria are summarized in Table 1.

Exclusion criteria

Patients meeting all preliminary eligibility criteria are considered potentially eligible for study. Patients are next screened for the presence of any specific exclusion which would preclude study entry. These exclusions are designed to eliminate patients for whom participation may be dangerous or patients with serious medical disorders whose impact on operative outcome may obscure the importance of nutritional, clinical and inflammatory factors. These are summarized in Table 2.

Default criteria

Once randomization has taken place, patients are removed from the study only for the following reasons: 1) patient’s or physician’s request, 2) Significant change in patient's treatment process, 3) create any exclusion criteria, 4) Sensitivity to pycnogenol supplementation.

Sample size

Sample size calculations were based upon Luzzi et al' s study (33) witch showed the mean CRP change in the treatment group was 60% and in the control was unchanged or Up to a maximum of 15%.

Based on The formula for comparing two proportions of a qualitative attribute from two independent statistical societies, sample size was determined 25 individuals in each group, (α= 0.05, β=0.1, the power of study is 90%).Assuming a probable drop in the sample, 30 patients in each group are considered.

Study procedures

The university's executive committee will oversee the project's implementation and progress, information security, safety of trial participants, and scientific impact assessment. Also this committee will review data from the trial. The trial sponsor will undertake auditing of the trial procedure.

Randomization and masking

We will randomly allocate eligible patients on enrolment (1:1) to either the control group or the intervention group. The randomization list of unique patient identifiers, is generated by the computer-generated random block size site. The classification is based on age (18 to 40 and 40 to 65 years old), gender (male / female) and APACHEII score (0 to 35 and 35 to 71) using quadruple blocks.

Nutritionist or clinicians will keep the sealed opaque envelope containing the unique patient identifier and the study group allocation in a locked cabinet in the study laboratory. They are opened by the second nutritionist. Investigators, all study staff hospital attending clinical teams, and patients were masked to the study group allocation.

Intervention

We do a pragmatic, parallel-group, double-blind, randomized controlled trial. We enroll 60 patients who are admitted to ICU at hospital of university in Tehran, Iran. All participants or their first degree relatives give informed consent to the clinician before participating.

Participants are randomly divided in two groups. The method of randomization and masking are explained above. At the first visit, baseline data are gathered and intervention group will receive pycnogenol supplement (OLIGOPIN) in the form oral capsules containing 50 mg pycnogenol plus 130 mg Microcrystalline Cellulose. OLIGOPIN powder of each capsule are dissolved in 10 ml deionized water and given to patients via gavage (3 capsule per day) for 10 days.

Control group will receive oral capsules containing 130 mg Microcrystalline Cellulose with 10 ml of deionized water via gavage (3 capsule per day) for 10 days.

The capsules are given by the investigator to the patients by gavage, so fidelity to the intervention will be strong, However for more certainty, at the end of each day, the number of capsules remaining for each patient will be checked.

In order to control the confounding effect of food intake, both the control group and the intervention group receive the standard formulas based on their daily required energy via enteral root feeding.

Possible risk assessment of intervention

Initially, an intervention with a dose of 150 mg of pycnogenol is started for 10 patients, and in the absence of clinical complications and observing the expected effect on the reduction of inflammatory markers, the same dose continues. Otherwise, it is reduced to 100 mg, if there is any adverse effect.

There have been no reports of serious adverse event in any clinical trials or commercial use of OLIGOPIN. However, these patients are regularly evaluated biochemically and clinically each day, and liver function test including serum levels of ALT (alanine aminotransferase) and AST (aspartate aminotransferase) checked. If there are any potential complications from intervention or, if the physician determines that the intervention should be discontinued, the supplements will be immediately removed from the patient's enteral nutrition.

Data collection

Data will be collected at four main times: at the base line, at 5th day of intervention, at 10th day of intervention and at the 28-day follow-up visit. At the base line demographic characteristics are gathered via a questionnaire. Anthropometric assessment including height (via ulna length), weight (by using portable scale “Balas”), body mass index and body composition (by using bio impedance device “Inbody”), are done at the base line, 5th day of intervention and at the end of intervention.

In order to evaluate inflammatory and oxidative stress markers, 10 cc of venous blood is taken from each patient at the base line, at the 5th day and at the end of the study. Then, the serum sample is isolated and used to measure the markers via ELISA kits. APACHE II (for assessment of clinical status of patients) and Nutric questionnaires (for assessment of nutritional status) filled out at the base line, 5th day and the end of study. SOFA questionnaire (for assessment of organ failure) filled out every other day. The mortality rate will be asked by phone within 28 days of the start of the intervention.

SPIRIT diagram of recommended content for the schedule of enrolment, interventions, and assessments shown in figure 1.

Data management

Specially designed forms are completed by study staff at each time point, and scanned, verified and committed to a local site database within 48 h of completion. Completed forms are stored as the source documentation in a locked cabinet, with access restricted to specified study team members. The forms are identified by unique participant ID number and do not contain any patient identifiable information. Queries based on data in the database are generated daily, including date, range and logic checks.

Outcomes

The measurable outcomes summarized in table 3.

Statistical methods

The trial profile will be summarized using a CONSORT flow chart, including reasons for non-eligibility and non-enrolment (34).

The objective of this clinical trial is to determine if pycnogenol supplementation improves clinical and nutritional outcome in TBI patients admitted in ICU or not. To answer this question, the outcome of

patients receiving PYC supplement will be compared with the outcome of patients receiving placebo.

All analyses will be conducted by initially assigned study arm in an intention-to-treat analysis, and adjusted for randomization site. Thus, all randomized patients who will receive at least one dose of study treatment and who will have both a baseline and at least one post baseline measurement will be analyzed. The data will be expressed as mean ± SD. Statistical analyses will be conducted with SPSS version 11.5 (SPSS Institute, Chicago, Ill). Chi-square test with Yates correction will be done for non-continuous variables for the prevalence study. Student t test will be done to assess the statistical significance of the continuous variables. Comparable nonparametric test (Mann-Whitney U test) will be substituted when tests for normality and equal variance failed. A value of P b .05 will be used as a criterion for statistical significance. Survival analysis will be performed with Kaplan-Meier test. The study design flow diagram summarized in figure 2.

Discussion

The purpose of this trial is to establish proof of concept of the efficacy of Oligopin in patients with TBI (GCS score 8). Patients will be screened and randomly enrolled into the intervention and control groups based on age, gender and APACHEII score.

Adding Oligopin to nutritional formula might reduce neuroinflammation and oxidative stress and improve clinical and nutritional status in TBI patients. But human study about pycnogenol (Oligopin) in this patients has not been done so far.

It is assumed, that oxidative stress mediated through the superoxide radical (superoxide) and other reactive oxygen species (ROS) may be principal to inflammation and impaired neural function (35). The acute inflammatory response differ in early and late stages of TBI; too much inflammation for too long delays recovery (36). Shortly after brain injury, there is mass production of proinflammatory cytokines, such as IL-1β, IL-6 and CRP (37).

In the event of TBI, IL-1β is the most studied cytokine. Glial cells produce IL-1β and affects neurons and other brain cells. IL-1β motivates inflammatory responses and aggregates immune cells, disrupts the BBB and forms edema, and leads to loss of neurons (38).The high level of IL-1β has been detected in CSF and brain tissue within early hours of brain injury in humans as well as in experimental animals (38). Administration of anti-IL-1β antibodies decreased edema and degradation of brain tissue. Improvement of cognitive function in rats following TBI (39). There are similar findings for IL-6. Intervention to mitigate IL-6 in animals with mild TBI, triggers normal brain function and reduces the effects of hypoxia (aggravation of inflammation of brain damage) (40). In TBI patients, CRP levels are correlated with the duration of hospitalization in ICU and dependence on the ventilator, and the severity of the damage is greater, the relationship is stronger (41). On the other hand, anti-inflammatory agents such as IL-10 have neuroprotective effects in TBI (42). Finally, we selected these inflammatory factors as outcomes of the study.

Duration of intervention

In this study we selected 10 days for intervention. Because according to the studies, the odds of survival in the first 10 days of admission of the patients in the ICU have a declining slope and after 10 days the slope of the decline will be milder (43, 44).Therefore, any intervention of treatment in this period (the first 10 days), which leads to a reduction in the risk of mortality, has great importance. On the other hand, duration of intervention has been used in clinical trials to evaluate the clinical effects of PYC supplementation has varied from several hours to several months (22, 45, 46). So in this study we expect to see the expected effects after 10 days.

Dose of supplementation

The average dose used in most human studies that has beneficial effects in improving inflammation is 150 milligrams (22, 47, 48).No side effects have been reported in this dose. Therefore we chose 150 mg Oligopin for this study.

Trial status
This trial is registered at clinicaltrials.gov (ref: NCT03777683) at December 17, 2018 and is on going. It is the first version of the protocol. In April 2019 recruitment began, and anticipated date to complete the study is February 2020.

Abbreviations

TBI: Traumatic brain injury

PYC: pycnogenol

APACHE II: The Acute Physiology and Chronic Health Evaluation

SOFA: The Sequential Organ Failure Assessment

Nutric score: Nutrition assessment in critically ill

ALT: alanine aminotransferase

AST: aspartate aminotransferase

CRP: C-reactive protein

IL-1β: Interleukin-1β

IL-6: Interleukin-6

IL-10: Interleukin-10

MDA: Malondialdehyde

TAC: Total antioxidant capacity

ROS: Reactive oxygen substrates

TGF-β: Transforming growth factor-beta

TNF-α: Tumor necrosis factor-α

MMPs: Matrix metalloproteinases

BBB: Blood- brain barrier

Declarations

Ethics approval and consent to participate

Central ethical approval has been confirmed from the Research Ethics Committees of the Mashhad University of medical sciences (ref approval no. IR.MUMS.MEDICAL.REC.1397.460) and we will not begin recruiting at other centers in the trial until local ethical approval has been obtained". All study procedures were in accordance with the ethical standards of the Helsinki Declaration. The informed consent will be obtained from all study participants and their guardians.

Availability of data and materials
Final study datasets will be stored locally and securely at Trauma and Injury Research Center, Iran University of medical sciences, Tehran, Iran for long-term storage and access. Participant level data will be made available by request on a case-by-case basis.

All Principal Investigators will access to the data sets. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

Consent for publication
Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

The trial is funded by the Mashhad University of medical sciences, and the Trauma and Injury Research Center of Iran University of medical sciences and was peer reviewed as part of the funding application process. These centers support all stage of study (the design of the study and collection, analysis, and interpretation of data and in writing the manuscript).

Author contribution

MM, OMM, MN and AN Designed research; *MM and OMM will* conduct research; MM and SF wrote the paper; AN had primary responsibility for final content. All authors read and approved the final protocol manuscript.

Acknowledgements

Thanks to the medical staff of the Hazrat Rasul Akram Hospital of Iran university of medical sciences, especially Dr. Mohammad Niyakanlahiji for helping us conduct this research project.

References

1. Galgano M, Toshkezi G, Qiu X, Russell T, Chin L, Zhao LR. Traumatic Brain Injury: Current Treatment Strategies and Future Endeavors. Cell transplantation. 2017;26(7):1118-30.
2. Peeters W, van den Brande R, Polinder S, Brazinova A, Steyerberg EW, Lingsma HF, et al. Epidemiology of traumatic brain injury in Europe. Acta neurochirurgica. 2015;157(10):1683-96.
3. Abdul-Muneer P, Chandra N, Haorah J. Interactions of oxidative stress and neurovascular inflammation in the pathogenesis of traumatic brain injury. Molecular neurobiology. 2015;51(3):966-79.
4. Williams AL. Traumatic brain injury. Physical Management for Neurological Conditions E-Book. 2018:153.
5. Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. Nature Reviews Neurology. 2013;9(4):231.
6. Menon D, Schwab K, Wright D, Maas A. Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health. Position statement: definition of traumatic brain injury. Arch Phys Med Rehabil. 2010;91(11):1637-40.
7. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. The Lancet. 1974;304(7872):81-4.
8. Gaetz M. The neurophysiology of brain injury. Clinical neurophysiology. 2004;115(1):4-18.
9. Beauchamp K, Mutlak H, Smith WR, Shohami E, Stahel PF. Pharmacology of traumatic brain injury: where is the “golden bullet”? Molecular medicine. 2008;14(11-12):731-40.
10. Lotocki G, de Rivero Vaccari JP, Perez ER, Sanchez-Molano J, Furones-Alonso O, Bramlett HM, et al. Alterations in blood-brain barrier permeability to large and small molecules and leukocyte accumulation after traumatic brain injury: effects of post-traumatic hypothermia. Journal of neurotrauma. 2009;26(7):1123-34.
11. Pun PB, Lu J, Moochhala S. Involvement of ROS in BBB dysfunction. Free radical research. 2009;43(4):348-64.

12. Toklu HZ, Hakan T, Bi ̇ ber N, Solakoğlu S, Öğünç AzV, Şener G. The protective effect of alpha lipoic acid against traumatic brain injury in rats. Free Radical Research. 2009;43(7):658-67.
13. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. BJA: British Journal of Anaesthesia. 2007;99(1):4-9.
14. Lucas SM, Rothwell NJ, Gibson RM. The role of inflammation in CNS injury and disease. British journal of pharmacology. 2006;147(S1):S232-S40.
15. Hall ED, Vaishnav RA, Mustafa AG. Antioxidant therapies for traumatic brain injury. Neurotherapeutics. 2010;7(1):51-61.
16. Anthonymuthu TS, Kenny EM, Lamade AM, Kagan VE, Bayır H. Oxidized phospholipid signaling in traumatic brain injury. Free Radical Biology and Medicine. 2018.
17. Rai VRH, Phang LF, Sia SF, Amir A, Veerakumaran JS, Kassim MKA, et al. Effects of immunonutrition on biomarkers in traumatic brain injury patients in Malaysia: a prospective randomized controlled trial. BMC Anesthesiology. 2017;17(1):81.
18. Wang X, Dong Y, Han X, Qi X-Q, Huang C-G, Hou L-J. Nutritional support for patients sustaining traumatic brain injury: a systematic review and meta-analysis of prospective studies. PloS one. 2013;8(3):e58838.
19. Peterik A, Milbrandt EB, Darby JM. Immunonutrition in critical illness: still fishing for the truth. BioMed Central; 2009.
20. Khorana J, Rerkasem K, Apichartpiyakul C, Sakonwasun C, Watcharasalcslip W, Waniyapong T, et al. Immunonutrition and cytokine response in patients with head injury. Medical journal of the Medical Association of Thailand. 2009;92(2):188.
21. Rohdewald PJ. Review on sustained relief of osteoarthritis symptoms with a proprietary extract from pine bark, Pycnogenol. Journal of medicinal food. 2018;21(1):1-4.
22. Gulati OP. Pycnogenol® in metabolic syndrome and related disorders. Phytotherapy Research. 2015;29(7):949-68.
23. Enseleit F, Sudano I, Periat D, Winnik S, Wolfrum M, Flammer AJ, et al. Effects of Pycnogenol on endothelial function in patients with stable coronary artery disease: a double-blind, randomized, placebo-controlled, cross-over study. European heart journal. 2012;33(13):1589-97.
24. Zhang Z, Tong X, Wei YL, Zhao L, Xu JY, Qin LQ. Effect of Pycnogenol Supplementation on Blood Pressure: A Systematic Review and Meta-analysis. Iranian journal of public health. 2018;47(6):779-87.
25. Rohdewald PJ. Review on Sustained Relief of Osteoarthritis Symptoms with a Proprietary Extract from Pine Bark, Pycnogenol. J Med Food. 2018;21(1):1-4.
26. Ansari MA, Keller JN, Scheff SW. Protective effect of Pycnogenol in human neuroblastoma SH-SY5Y cells following acrolein-induced cytotoxicity. Free radical biology and medicine. 2008;45(11):1510-9.
27. Peng Q, Buz'Zard A, Lau B. Pycnogenol® protects neurons from amyloid-β peptide-induced apoptosis. Molecular Brain Research. 2002;104(1):55-65.

28. Sahebkar A. A systematic review and meta-analysis of the effects of pycnogenol on plasma lipids. Journal of cardiovascular pharmacology and therapeutics. 2014;19(3):244-55.
29. Hadi A, Pourmasoumi M, Mohammadi H, Javaheri A, Rouhani MH. The impact of pycnogenol supplementation on plasma lipids in humans: A systematic review and meta-analysis of clinical trials. Phytotherapy research : PTR. 2018.
30. Scheff SW, Ansari MA, Roberts KN. Neuroprotective effect of Pycnogenol® following traumatic brain injury. Experimental neurology. 2013;239:183-91.
31. Ishrat T, Parveen K, Hoda MN, Khan MB, Yousuf S, Ansari MA, et al. Effects of Pycnogenol and vitamin E on cognitive deficits and oxidative damage induced by intracerebroventricular streptozotocin in rats. Behavioural pharmacology. 2009;20(7):567-75.
32. Oliff H. Scientific and clinical monograph on Pycnogenol®. The American Botanical Council. 2009.
33. Luzzi R, Belcaro G, Hosoi M, Feragalli B, Cornelli U, Dugall M, et al. Normalization of cardiovascular risk factors in peri-menopausal women with Pycnogenol®. Minerva Ginecol. 2017;69(1):29-34.
34. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux P, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. The BMJ. 2010;340.
35. Kim H, Ahn JH, Song M, Kim DW, Lee T-K, Lee J-C, et al. Pretreated fucoidan confers neuroprotection against transient global cerebral ischemic injury in the gerbil hippocampal CA1 area via reducing of glial cell activation and oxidative stress. Biomedicine & Pharmacotherapy. 2019;109:1718-27.
36. McGuire MF, Savarraj JP, Kitagawa RS, Choi HA. Acute Inflammation After Traumatic Brain Injury. Translational Inflammation: Elsevier; 2019. p. 221-39.
37. Vaughan LE, Ranganathan PR, Kumar RG, Wagner AK, Rubin JE. A mathematical model of neuroinflammation in severe clinical traumatic brain injury. Journal of neuroinflammation. 2018;15(1):345.
38. Muballe KD, Sewani-Rusike CR, Longo-Mbenza B, Iputo J. Predictors of recovery in moderate to severe traumatic brain injury. Journal of Neurosurgery. 2018;1(aop):1-10.
39. Clausen F, Hanell A, Israelsson C, Hedin J, Ebendal T, Mir AK, et al. Neutralization of interleukin-1beta reduces cerebral edema and tissue loss and improves late cognitive outcome following traumatic brain injury in mice. The European journal of neuroscience. 2011;34(1):110-23.
40. Yang SH, Gangidine M, Pritts TA, Goodman MD, Lentsch AB. Interleukin 6 mediates neuroinflammation and motor coordination deficits after mild traumatic brain injury and brief hypoxia in mice. Shock (Augusta, Ga). 2013;40(6):471-5.
41. Naghibi T, Mohajeri M, Dobakhti F. Inflammation and Outcome in Traumatic Brain Injury: Does Gender Effect on Survival and Prognosis? Journal of clinical and diagnostic research: JCDR. 2017;11(2):PC06.
42. Chen X, Duan X-S, Xu L-J, Zhao J-J, She Z-F, Chen W-W, et al. Interleukin-10 mediates the neuroprotection of hyperbaric oxygen therapy against traumatic brain injury in mice. Neuroscience. 2014;266:235-43.

43. Lilly CM, Cody S, Zhao H, Landry K, Baker SP, McIlwaine J, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. Jama. 2011;305(21):2175-83.
44. Strand K, Walther SM, Reinikainen M, Ala-Kokko T, Nolin T, Martner J, et al. Variations in the length of stay of intensive care unit nonsurvivors in three Scandinavian countries. Critical care. 2010;14(5):R175.
45. Schäfer A, Chovanová Z, Muchová J, Sumegová K, Liptáková A, Ďuračková Z, et al. Inhibition of COX-1 and COX-2 activity by plasma of human volunteers after ingestion of French maritime pine bark extract (Pycnogenol). Biomedicine & Pharmacotherapy. 2006;60(1):5-9.
46. Cesarone M, Belcaro G, Rohdewald P, Pellegrini L, Ippolito E, Scoccianti M, et al. Prevention of edema in long flights with Pycnogenol®. Clinical and applied thrombosis/hemostasis. 2005;11(3):289-94.
47. Gulati OP. Pycnogenol® in chronic venous insufficiency and related venous disorders. Phytotherapy research. 2014;28(3):348-62.
48. Cesarone MR, Belcaro G, Stuard S, Schönlau F, Di Renzo A, Grossi MG, et al. Kidney flow and function in hypertension: protective effects of Pycnogenol in hypertensive participants—a controlled study. Journal of cardiovascular pharmacology and therapeutics. 2010;15(1):41-6.

Tables

Table 1. primary criteria for study eligibility

Admission in ICU [a] due to TBI [b]
18 year ≤ age ≤ 65 year
GCS [c] score 8
Stable hemodynamic and metabolic status in the first 24 to 48 hours
Having enteral nutritional support
Fill out the informed consent form by the patient or first-degree relatives of the patient

[a] Intensive care unit. [b] Traumatic brain injury. [c] Glasgow coma scale.

Table 2. exclusion criteria

Pregnancy and lactation
Morbid obesity: BMI [a] ≥ 40
Failure to start enteral nutrition in the first 24-48 hours
Suffering from autoimmune disorders and HIV/Aids
Suffering or having History of cancer and any liver failure
Receiving positive inotropic medications including Dopamine, Dobutamine and Epinephrine
Severe and active bleeding
Suffering from Sepsis
Having history of known food allergies

[a] Body mass index.

Table 3. measurable outcomes

outcome	Time Frame	Measurement method
Change of inflammatory markers: IL-6 , IL-1β	5 and 10 days	ELISA kit
Change of inflammatory marker: CRP	5 and 10 days	Auto analyzer
Change of anti- inflammatory marker: IL-10	5 and 10 days	ELISA kit
Change of oxidative stress markers: Malondialdehyde, total anti-oxidant capacity	5 and 10 days	ELISA kit
Change of weight	5 and 10 days	Portable scale “Balas”
Change of body fat percentage	5 and 10 days	Bio impedance device “Inbody”
Change of body mass index	5 and 10 days	Equation
Change of APCHE[a] score	5 and 10 days	APCHE score questionnaire
Change of SOFA[b] score	1, 3, 5, 7, 9, 10 day	SOFA score questionnaire
Change of Nutric score	5 and 10 days	Nutric score questionnaire
28-day mortality	28 days	Telephone fallow up

[a] acute physiologic and chronic health evaluation II. [b] sequential organ failure assessment.

Figures

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	-24h to 48h	0	Day1	Day 3	Day 5	Day 7	Day 10	Day 28
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
medical history	X							
Allocation		X						
INTERVENTIONS:								
Intervention pycnogenol			←	—	—	—	→	
Intervention placebo			←	—	—	—	→	
ASSESSMENTS:								
inflammatory markers			X		X		X	
anti- inflammatory marker			X		X		X	
oxidative stress markers			X		X		X	
weight			X		X		X	
body fat percentage			X		X		X	
body mass index			X		X		X	
APCHEII [a] score			X		X		X	
SOFA [b] score			X	X	X	X	X	
Nutric score			X		X		X	
28-day mortality								X

[a] acute physiologic and chronic health evaluation II. [b] sequential organ failure assessment.

Figure 1

SPIRIT diagram of recommended content for the schedule of enrolment, interventions, and assessments

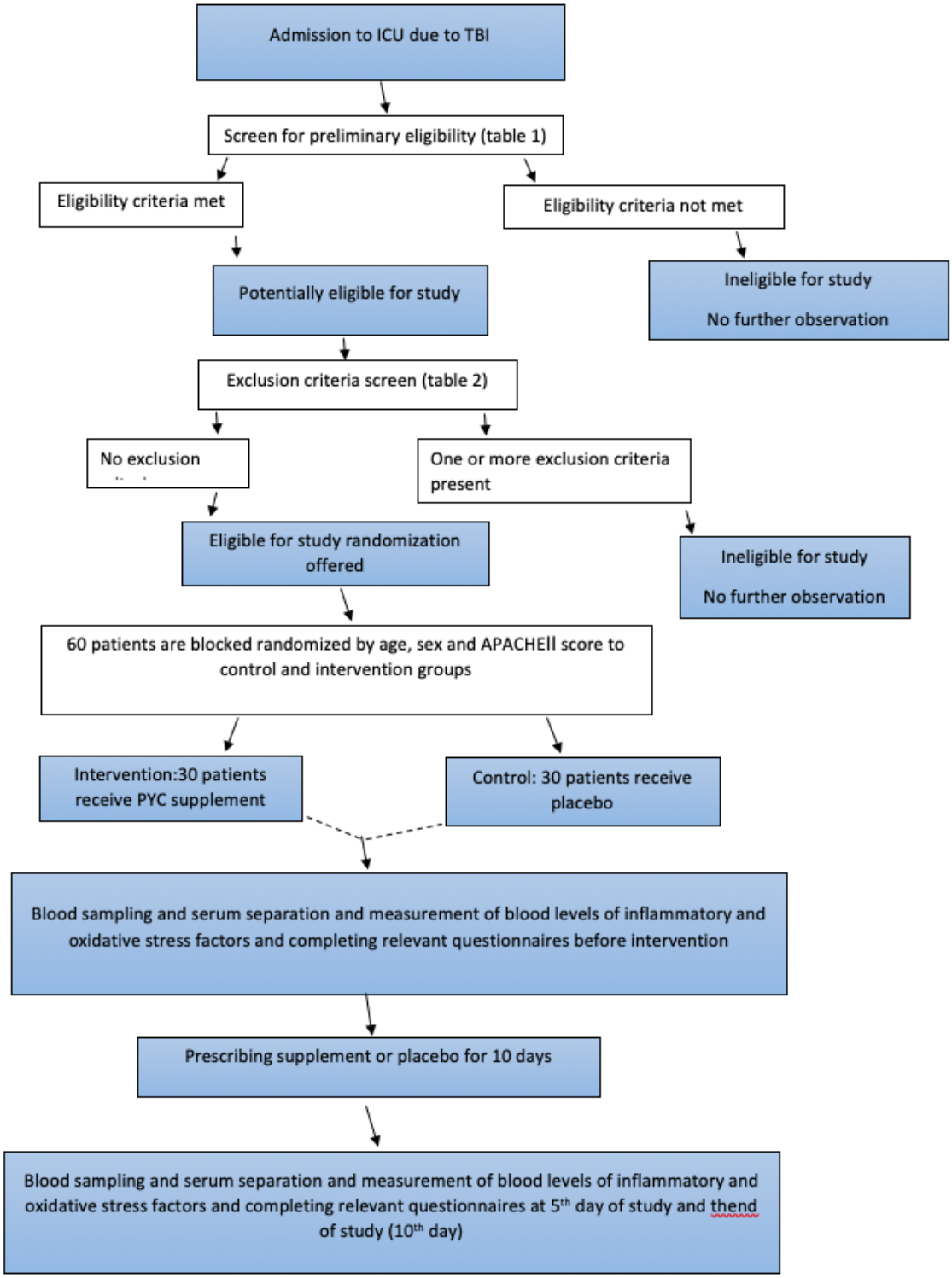

Figure 2

Study design flow diagram

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.doc