Chapter

Use of Neuroprotective agents for Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is the leading cause of mortality and morbidity especially in young ages, while over 30 years of neuroprotective agents use for TBI management provided neither any recommended agent for favorable outcome nor less adverse effects in TBI management yet. This review got selected keywords' search and ran in known international and local databases, with no limitation up to September 6, 2015. Related to the subject, clinical human studies have been selected for the review. Data from 32 studies were classified into 10 subgroups. About 18 studies with a population of 4637 participants were included in 6 topic reviews and meta-analyses. Oxygen use in acute management of TBI to reduce mortality rates could be recommended. Corticosteroid use in solo acute TBI management is prohibited due to increasing risk of mortalities. However, in dual-diagnosed patients (TBI and spinal cord injury (SCI) together), corticosteroid use should be obtained by a Bracken protocol. The use of citicoline in acute TBI is no more supported. The use of cyclosporine-A for ICP control depends on the resources and physician's decision. Rivastigmine use for chronic neurocognitive conditions of TBI management had some beneficence in severely impaired participants. However, the use of other agents in TBI has no field of support yet.

Keywords: traumatic brain injury, head injury, neuroprotective agents, systematic review, meta-analysis

1. Introduction

1.1 Description of the condition

Traumatic brain injury (TBI), which is also known as head injury [1–3], is the leading cause of mortality and morbidity [1, 4–6], especially in young ages [1]; that is defined as "the occurrence of injury to the head, that is, associated with symptoms or signs attributable to the injury such as decreased level of consciousness, amnesia, other neurological or neuropsychological abnormalities, skull fracture, intracranial lesions or death." [6].

Epidemiological studies, demonstrate following statements in USA [4];

- The incidence rate of 558 cases per 100,000 person each year,
- TBI related disability estimated as 33 new cases per 100,000 people in a year,
- More than 50,000 deaths each year,
- Motor vehicle collisions (MVC) is the responsible for 50% of TBI causes, following by falls (38%), and violence (also including attempted suicide) 4%,
- TBI costs more than $48 billion a year. About 2.5 and 6.5 million Americans alive today have had a TBI assault. “Survivors of TBI are often left with significant cognitive, behavioral, and communicative disabilities” [7]. According to the chronology period and the state of the condition, it categorizes under “Primary” and “Secondary” injury [1].

1.2 Description of the intervention

According to medical subheadings (MeSH) definition, Neuroprotective agents are “Drugs intended to prevent damage to the brain or spinal cord from ischemia, stroke, convulsions, or trauma. Some must be administered before the event, but others may be effective for some time after. They act by a variety of mechanisms, but often directly or indirectly minimize the damage produced by endogenous excitatory amino acids” [8]. As mentioned in the MeSH definition, there are variety of drugs and their action mechanisms to minimize the TBI damage; the breadth list of trials on www.clinicaltrial.gov for “Neuroprotective Agents” and “Traumatic Brain Injury” terms, states this. A recent study of Burns et al. declared 30 years of using Neuroprotective agents on animal models forecasting the same effect on humans failed, and represents to use animal models as new cases for stem cell studies as well, rather than formerly known for using Neuroprotective agents [9], which is confirmed by other studies too [10, 11].

The recent challenging review and meta-analyses study of Leucht et al. about efficacy of commonly used major drugs for medical and psychological conditions, seems to be a practice-challenging article for all physicians over the world [12]; this meta-analyzed article’s results on major commonly used drugs showed the small to medium effect of 13 drugs and nearly medium to favorable effect of 3 drugs out of 19 major commonly used drugs for variety of clinical or mental conditions; collecting these information together rings a bell; how to use the most effective interventions for conditions?

2. Literature review

There are wide variety of Neuroprotective agents, and breadth studies on human and animal cases, the following lists the agents which were studied on human clinical trials:

2.1 Oxygen

The vital element of life and viability of neurons. Hypoxia leads to anaerobic metabolism, acidosis, and reduction in cellular metabolism. Neurons messaging conduction ability disturbs due to loss of their ability to maintain ionic homeostasis.

Free oxygen radicals also accumulate and degrade cell membrane; which all if lead to irreversible changes in neuron cells, it "results in unavoidable cell death." There are also Cochrane reviews for hyperbaric oxygen (HBO_2) and hyperventilation (NBH) use in TBI [1, 2].

2.2 Corticosteroids

Inflammatory process after TBI, which causes brain edema and intracranial pressure (ICP) rise, performed the hypothesis of using corticosteroids for TBI, the primary researches and studies showed the beneficial effect of this intervention, while CRASH trial in 2005 and an updated Cochrane review after that, challenged the efficacy of corticosteroids use for TBI [4]; further from this study's proposal, steroids using for spinal cord injury (SCI) seems to have beneficial effects; also there is a Cochrane review for its neuroprotection beneficence in SCI assaults [13].

2.3 Progesterone

It has a wide variety of neuroprotection mechanisms of action, as an antioxidant agent, by reducing brain edema and inflammatory-related factors, controlling of vasogenic edema through blood brain barrier (BBB) reconstitution and aquaporin-4 water transporter modulation, axonal regenerating stimulant, inhibition of inflammatory cytokines production, synaptogenesis and dendritic arborization, altering glutamate receptor activity to reduce excitotoxicity of injury and also taking all these effects by its receptor's key rolling [14–16]. Also inhibition of ion flux cell pores like L-type calcium channel, potassium, and sodium voltage-gates, as well GABA-A receptors, all result in vasoconstriction and reducing edema that seem likely to dihydropyridine's mechanism of action, without its side effects like dizziness, peripheral edema, hypotension, reflex tachycardia and headaches [17, 18].

2.4 Monoaminergic agents

Amphetamine and other promotors of neuroaminergic neurotransmission have been suggested to improve the functional recovery of the brain after TBI. There is also a Cochrane review for these agents [19].

2.5 Erythropoietin (EPO)

A glycoprotein hormone of cytokine type-I super family, that its anti-apoptotic and anti-inflammatory properties, also interaction of EPO with neural voltage-gated calcium channels, and EPO with EPO-receptors increasing of local production after TBI, seems to be EPO's mechanisms of action [20–22].

2.6 Magnesium sulfate and other magnesium salts

Reduction in serum magnesium levels after TBI, and beneficial effects of magnesium therapy in animal models, conceptualized its use for human cases, its failure in recent studies, came to the conclusion of blood brain barrier (BBB) effect on this agent's transmission [23].

2.7 Cerebrolysin

"Cerebrolysin is a peptide-preparation, produced by the bio-technologically standardized enzymatic breakdown of purified porcine brain proteins." mechanism

of action is not fully understood, but animal studies, suggest improved neuronal oxygen utilization, reduction of cerebral lactic acid concentration and free oxygen radical concentrations [24].

2.8 Citicoline (CDP-choline) and other cholinergics

Adenosine tri-phosphate (ATP) is responsible for cell membrane sodium-potassium (Na-K) ATPase pump's function; TBI related cell membrane un-integrity and accumulation of extracellular water, leads to the known brain edema, also formation of lipid peroxidase. Cholinergic agents' effects in cell-oxygenation cycles and formation of ATP indirectly may cause cell wall integrity formation as well as prevent further secondary injuries [25].

2.9 NeuroAid

A Chinese medicine, also known as MCL601 and MCL901 (a.k.a. Simplified to NeuroAid or NeuroAid-II, respectively), which showed Neuroprotective effects in stroke trials [26, 27].

2.10 Cyclosporine A (CsA)

Preservation of mitochondrial function after TBI is the recommended mechanism of action for this agent [28, 29].

2.11 Rivastigmine

Mostly known for its cholinesterase inhibitory (ChE-inh) effects, that improves cholinergic function of brain in Alzheimer disease (AD) trials; there are also TBI trials based on hypothesis of post-traumatic cholinergic deficiencies [30, 31].

2.12 Piracetam

This intervention seems to improve neurocognitive state of patients without any remarkable effects on the mortalities.

2.13 Anti-epileptic drugs

Anti-epileptic drugs may have some Neuroprotective effects as well, but they are not included in this study, however these drugs have their own Cochrane review [3].

2.14 Why it is important to do this review?

The review, been performed on Neuroprotective agents for TBI, fulfill the systematic review & analysis on each one of the mentioned agents in "Literature Review" section of this study; "Drug data is complex and requires thoughtful consideration regarding which medication and therapies are best suited for certain situation and patients." Leucht et al. declared [12]. Burns et al. work didn't clearly demonstrate the use of new stem cell studies on TBI, but it has hopes for SCI [9]. Studies showed people may not feel comfortable with stem cell therapies because of "don't want to get the risk of cancer" or "don't want to have another surgery" who also are about 58–63% of patients [9] that may lead our current hopes to neuroprotective use, despite stem cells.

3. Methods

Criteria for considering studies for this review.

3.1 Types of studies

The back-bone of present study's meta-analyses made by including RCTs, which their reporting quality, compared to CONsolidated Standards Of Reporting Trials (CONSORT-statement) 2010 (http://www.consort-statement.org/); other related to subject articles, with good and qualitative methods in reporting, included according to the study's statistical consultant's point of view. Guidelines or protocols, letter to editors and systematic reviews are excluded from the data analyses.

3.2 Types of participants

Humans of any age, and with any severity (mild, moderate, severe) of focal or diffuse TBI, have been included; neither animal studies nor pre-clinical (in-vivo) trials included in this study.

3.3 Types of interventions

The related studies about the mentioned agents in "Literature Review" section with any frequency, any chronicity and any mode of use.

3.4 Types of outcome measures

Outcomes were analyzed in two main groups for acute TBI management:

3.4.1 Primary outcomes

- Mortality and vegetative state
- Good recovery and mild disability

As measured by Glasgow Outcome Scale (GOS) or Extended Type (GOS-E) after 3–6 months of patient follow-up; severe disabilities weren't included in the analyses.

3.4.2 Secondary outcomes

- Any adverse effects or events of interventions during the trial.

For chronic TBI management, outcomes were mostly analyzed for neurocognitive state.

3.5 Search methods for identification of studies

The search strategy was not restricted by language, date, participants race, gender or publication status; but date limitation implemented to the referencing databases (i.e., SCOPUS and Thomson Reuters Web of Science) for after 2000 search results, also limiting results to human studies where possible.

3.5.1 Electronic searches

The web-based searched data-bases are:

- Cochrane CENTRAL (September 6, 2015)
- MedLine through PUBMED (September 6, 2015)
- SCOPUS (September 6, 2015)
- Thomson Reuters Web of Science (September 6, 2015)
- SID.ir (September 6, 2015)
- Barekat Knowledge Deployment Foundation (formerly known as IRAN-MEDEX) (September 6, 2015)
- ClinicalTrials.gov (September 6, 2015).

3.5.2 Searching other resources

Other related articles, came out through Internet search for full-text articles, and full-text requests through www.researchgate.net, and skimming in bibliographies of articles. Also contacting with experts to enrich the including data.

3.6 Data collection and analysis

Zotero v.4.0.28 (available from www.zotero.org) was used as Reference Manager of this review, while Cochrane's Review Manager (RevMan v5.3) taken the role of meta-analyses and conducting the whole study as well.

3.7 Selection of studies

Screening of related articles via their titles and abstracts done by two review authors (AM and MM); further assessment of including articles obtained by applying CONSORT-statement 2010 on full-texts of the articles by two review authors (HSB and MM), also disagreements of the screening-phase articles and the decision to include non-RCT studies referred to statistical consultant of study (HSB). The Preferred Reporting Items for Systematic Reviews & Meta-Analyses (PRISMA) statement, lead authors to diagram the process of study-selection (**Figure 1**).

3.8 Data extraction and management

Two review authors (AM and MM) extracted data from the included studies using CONSORT 2010 characteristics; any disagreements, referred to the third author (HSB).

3.9 Assessment of risk of bias in included studies

Two review authors (HSB and MM) assessed RCTs using the "risk of bias" assessment tool of "Cochrane Handbook for Systematic Reviews of Interventions v. 5.1.0" [32].

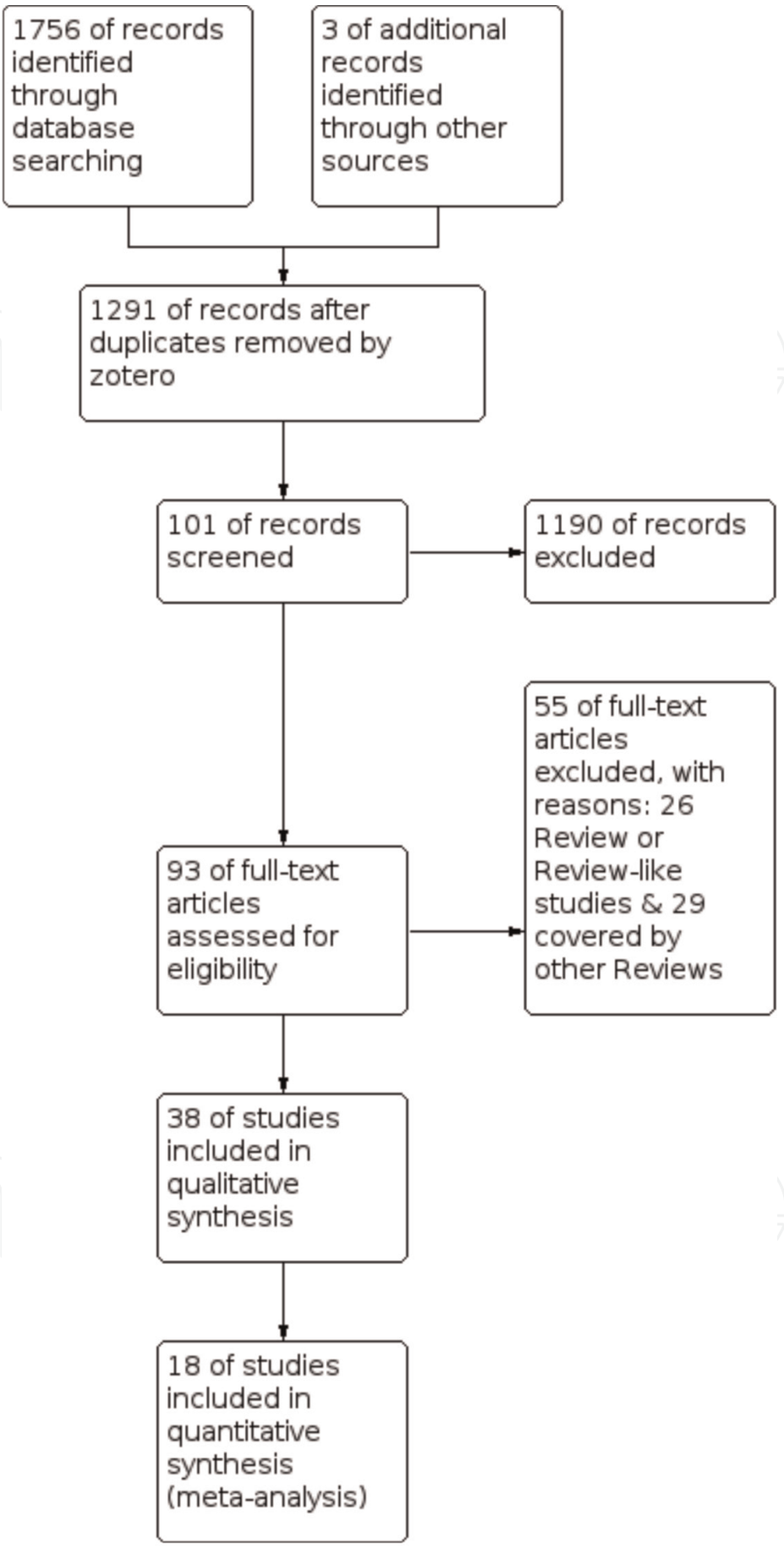

Figure 1.
PRISMA template (study flowchart).

3.10 Measures of treatment effect

Glasgow Outcome Scale (GOS) or its Extended type used as the assessment tool for severe TBIs outcome, considered to take place in the analyses; otherwise, patients preference of interventions [i.e., patient reported outcome (PRO)] in studies' results, were taken as outcome measurements of included studies in mild and moderate TBIs. More information of each intervention outcome analysis is represented under "Results" section of the study.

3.11 Unite of analysis issues

All meta-analyses of fixed effects model for dichotomous quantitative results, done by their risk ratio and confidence interval (CI) = 95%; continuous data results analyzed by their mean difference and CI = 95%; random effects model applied if $I^2 > 50\%$ [33].

3.12 Dealing with missing data

According to search strategy, authors have to conclude as possible as the available studies for the review, reduce selection and information biases as well; but some data would never been available even after contacting the original investigators or correspondence authors; the authors strategy for dealing with these kind of missing data was to ignore the missing data and to analyze only the available data, but if it's assumed that the missing data, had a huge effect on the analysis, in the HSB's point of view, using statistical models to allow missing data in analysis, making assumptions about their relationships with the available data were taken, fortunately there was no such conflict during this study's process.

3.13 Assessment of heterogeneity

Any heterogeneity of studies referred to HSB, for statistical consultant's point of view to reassess their use in the study, if they didn't have the availability to take part in study, they had been excluded.

3.14 Assessment of reporting biases

Probable reporting biases of studies, reported by using "Cochrane Handbook for Systematic Reviews of Interventions v. 5.1.0" method [32].

3.15 Subgroup analysis and investigation of heterogeneity

Data analyses based on:

- Favorable outcome of intervention (mostly based on GOS or GOS-E);
- Mortality and vegetative-state analysis
- Probable side-effects of interventions.

If some interesting results of study(ies) are brought, they'd be analyzed separately.

3.16 Sensitivity analysis

All of the search studies results reporting, were based on significant meaningful of results with $p < 0.05$ and CI = 95%.

4. Results

4.1 Description of studies

Qualitative report of study results, was completed with RCTs meta-analyses. Which from 38 RCTs included in this study, 18 RCTs been meta-analyzed. Also previous review papers in this field covered RCTs which are not included in this review again, i.e., 27 of these RCTs were discussed by Alderson et al. Cochrane review of corticosteroids [4]; Monoaminergic agents Cochrane review by Forsyth et al. covered 20 of them [19]. However previously discussed papers in HBO_2 and NBH Cochrane reviews, didn't take part in this review again [1, 2], which limited oxygen topic's studies to seven papers and no new articles found for those other two topics; **Figure 1** and **Table 1** summarize the finding information. The 18 included meta-analyzed studies, have a population of 4637 patients, of which 3650 patients were for four new phase-III RCTs altogether. Furthermore information is available under each topic of "Results of the search" section.

4.2 Results of the search

4.2.1 Oxygen

This intervention is the most eligible one of all other experimental trials of TBI neuroprotectives. Two Cochrane reviews were conducted under the title

Neuroprotective	Total no. RCTs	No. RCTs in this study	No. RCTs included	No. acute TBI RCTs	No. chronic TBI RCTs	Studies populations	No. phase-3 RCTs
Oxygen	24	7	4	1	3	205	0
Corticosteroid	27	All study results from Alderson 2006 Cochrane review [4]					
Progesterone	7	7	4	4	–	2320	2
Monoaminergics	20	All study results from Forsyth 2011 Cochrane review [19]					
Erythropoietin	4	4	2	2	–	645	1
Magnesium	4	1	Vink et al. [23] results combined with this pilot study				0
Cerebrolysin	1	1	1	1	–	32	0
Citicoline	4	4	4	3	1	1196	1
NeuroAid	0	0	0	0	0	0	0
Cyclosporine A	5	5	2	2	–	89	0
Rivastigmine	3	3	1	–	1	157	0
Piracetam	3	0	0	unknown	unknown	unknown	unknown
Miscellaneous	unknown	6	0	–	–	–	–
Total	**102**	**38**	**18**	**13**	**5**	**4637**	**4**

Table 1.
Neuroprotective RCTs for TBI at a glance.

"Hyperventilation therapy for acute traumatic brain injury (Review)," which established in 1997 and continued till the last updated paper of 2009 [2], and "Hyperbaric Oxygen therapy for the adjunctive treatment of traumatic brain injury (Review)," which started from 2004 and was last revised in 2012 [1]. These reviews demonstrated reduction in mortality rates while using oxygen in TBI, but there was no adequate evidences to support better clinical outcomes. This review's search results got eight more new additional studies. One observational study to investigate guideline adherence about pre-hospital advanced airway attempt for oxygenation in 54 severe TBI patients, that resulted in good adherence of performers to the guidelines [34], which also reported in other studies aimed to assess practitioners' adherence to guidelines, even better if they were supported by strong evidences [35, 36], but not satisfied results which recommended revision for guidelines; and seven clinical trials, mostly case-sham control design method, that five of them were pilot phase-II studies supported by Department of Defense/Veteran Affair (DoD/VA) for a huge phase-III RCT on HBO_2 use [37–41], the other two trials were Rockswold et al. and Boussi-Gross et al. for combined HBO_2/NBH treatment and HBO_2 in a case control and cross-over method trials respectively [42, 43]. Except than Rockswold et al. study on acute TBI patients, other studies' participants were of chronic impaired TBI patients.

Overall patients analyses without loss to follow-ups are 205 patients as 48 in Wolf et al., 42 in Rockswald et al., 56 in Boussi-Gross et al. and 59 in Cifu et al.; This review, include all of these trials in narrative review, but because of their heterogeneity in reporting outcomes, no meta-analysis conducted for the results [37, 40, 42, 43].

The only study reported mortality was Rockswold et al. for 16% in HBO_2/NBH combined group and 42% in control group, that might be due to its acute phase design for TBI management [43] in comparison to other three trials were about mild chronic TBI management. Boussi-Gross et al. study reports significant improvements in cognitive states (memory, attention, executive function, information processing speed) of patients with mild TBI in chronic phase, while DoD/VA related studies didn't state any significant changes of cognitive functions between HBO_2 and sham-control groups according to their Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) and Post-Traumatic Stress Disorder Check List-Military (PCL-M) assessment tools [37, 40, 42]; Rockswald et al. acute phase study's GOS outcome for HBO_2/NBH combined group, demonstrated significant improvements (p = 0.024), and better outcomes for cerebral metabolism, partial oxygen pressure in brain and ICP [43].

Also only side-effect report was in Wolf et al. study that ear barotrauma and headache were the most common conditions [41], while Cifu et al. study on eye tracking abnormalities didn't demonstrate any significantly meaningful improvements for HBO_2 treatment participants, Wolf et al. results on Snellen chart assessment of visual acuity showed improvements in both HBO_2 and Sham-control groups (22 of 47 eyes and 25 of 46 eyes respectively), also reduction of visual acuity was less in the sham-control group (6 of 47 eyes and 3 of 46 eyes) [39, 41].

4.2.2 Corticosteroids

Cochrane updated review for corticosteroids in 2006, recommended no more trials of corticosteroids for TBI according to phase-III CRASH trial's results, another

update of this review at January 7, 2009, found no novel study to investigate. There was no more study in current review's search results too.

4.2.3 Progesterone

The 2012 Cochrane review of "Progesterone for acute traumatic brain injury (Review)," based on three phase-II trials, declared that it would be updated as two more multi-centric clinical trials' results came out [5]; at the time of current review's searching for Neuroprotective agents, those mentioned trials and one more study been achieved [10, 11, 44]. Authors complete reading each one of the studies by comparing them to CONSORT 2010 checklist, finally included four studies [10, 11, 45, 46] and excluded three of them [44, 47, 48].

Included studies consisted of 2320 cases (1192 in progesterone group and 1128 in placebo-control group); SYNAPSE study and ProTECT-III respectively by Skolnick et al. and Wright et al. (in 2014) are the new phase 3, multi-centric, RCTs with the weight of 93.5% of whole cases [10, 11]. ProTECT-III halted in its secondary interim analysis, but SYNAPSE completed the predicted proposal and consists 51.5% of cases.

The analyses of favorable intervention outcome and mortality in these studies based on GOS report analysis in current method: favorably outcome (good recovery and moderate disability), mortality (vegetative state and death), the severe disability didn't included in the analysis. All of these studies analyzed their outcomes in a 6 month period but Wright et al. (in 2007), had a follow-up of 30 days [10, 11, 45, 46].

Intervention's side-effects also analyzed as the most happened for patients in each group as a whole but not on each of the side-effects solely. Also two studies didn't take part in this analysis. Skolnick et al.'s outcome results for adverse effects were different from case-control group's total number. It seems that five cases from control group have been analyzed in case group. An E-mail has been sent to the corresponding author for this confusing part, but till date, there is no reply [11]. Xiao et al. reported no adverse effects for the intervention [46].

The analyses showed no significant differences between progesterone and placebo groups in favorable treatment [(p = 0.75; RR 1.02, 95% CI 0.88–1.19; participants = 2320; studies = 4; I^2 = 53%) **Figure 2**], neither in mortalities [(p = 0.21; RR 0.77, 95% CI 0.50–1.17; participants = 2320; studies = 4; I^2 = 82%) **Figure 3**], nor in adverse effects analysis [(p = 085; RR 1.03, 95% CI 0.72–1.48; participants = 982; studies = 2; I^2 = 87%) **Figure 4**].

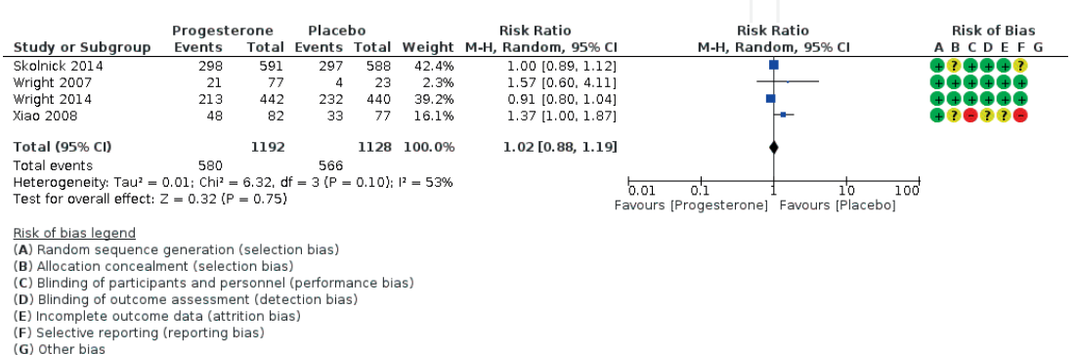

Figure 2.
Progesterone favorable outcome.

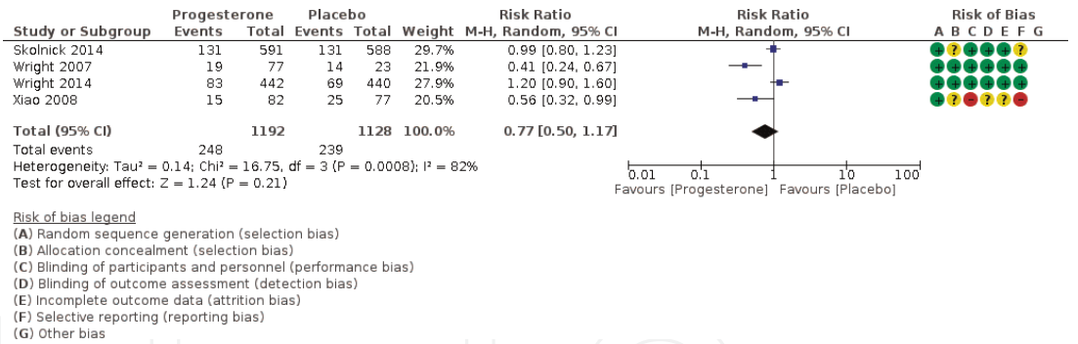

Figure 3.
Progesterone mortality.

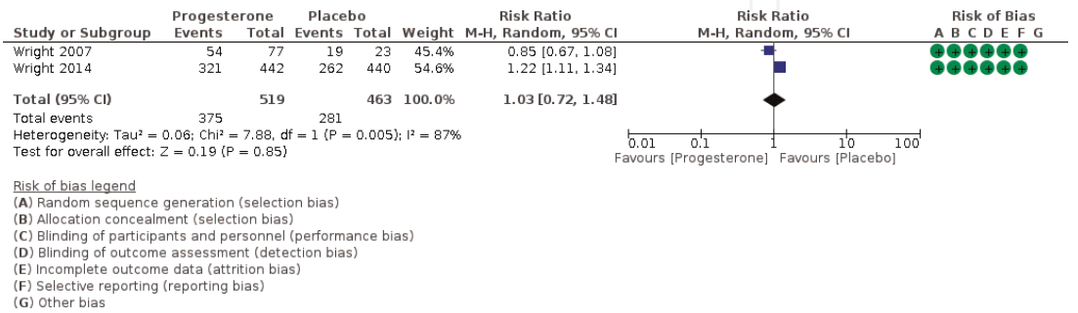

Figure 4.
Progesterone adverse-effects.

4.2.4 Monoaminergic agents

The Cochrane review of "Monoaminergic agonists for acute traumatic brain injury," first established in 2006, and updated later on, till its last update was in 2011 didn't included any studies [19]. Search results didn't collect any new studies.

4.2.5 Erythropoietin (EPO)

The primary search results for this topic, consists of a review on in-vitro and in-vivo studies till 2009 [49]. One retrospective case-control study [50] and four prospective RCTs [20, 22, 51, 52]; two of these studies were reports of a same phase-III multi-centric placebo-control trial known as EPO-TBI, and Nichol et al.'s reporting was more complete than the other one, which persuades authors to exclude Presneil et al. from quantitative analysis [21, 22]. Abrishamkar et al.'s paper has been excluded from meta-analysis too, due to its restricted study design on male patients [20].

The whole studies population analysis related to Aloizos et al. and Nichol et al. were 645 patients [21, 51]. Both studies followed patient up to 6 months analyzing total better outcomes of patients showed no significant difference between study groups [(p = 0.30; MD 1.22, 95% CI −1.09–3.53; participants = 638; studies = 2; I^2 = 99%) **Figure 5**], also EPO-TBI trial's GOS reporting outcome showed no significant difference too [(p = 0.90; RR 1.01, 95% CI 0.87–1.17; participants = 596; studies = 1; I^2 = 0%) **Figure 6**]. Mortality and vegetative-state analysis, was significantly skewed toward intervention group [(p = 0.04; RR 0.65, 95% CI 0.43–0.98; participants = 644; studies = 2; I^2 = 0%) **Figure 7**]; while side-effect analysis showed nearly significant less vascular side effects in intervention group [(p = 0.06; RR 0.86, 95% CI 0.73–1.00; participants = 603; studies = 1; I^2 = 100%) **Figure 8**] and no significant difference in non-vascular side-effects between two groups of EPO-TBI

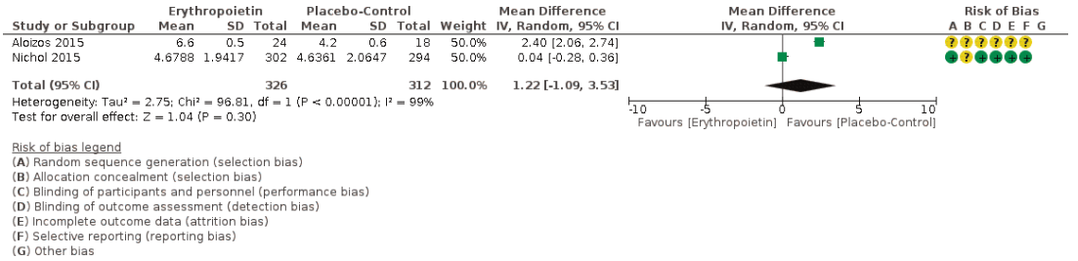

Figure 5.
Erythropoietin total outcome assessment.

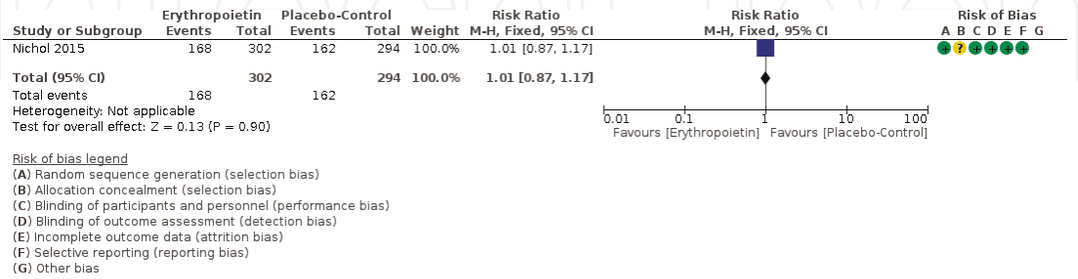

Figure 6.
Erythropoietin favorable outcome.

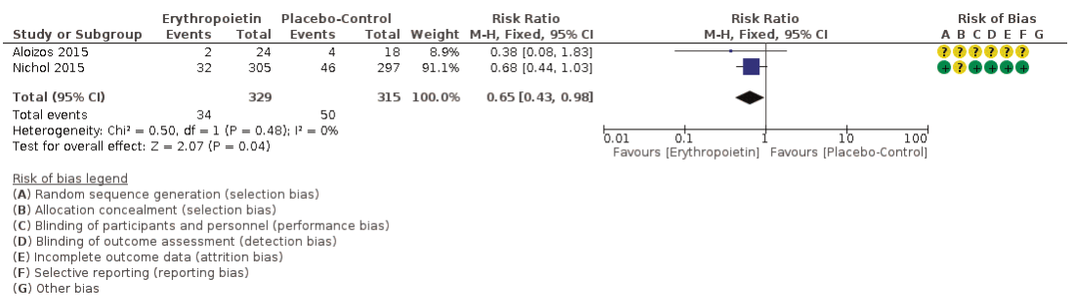

Figure 7.
Erythropoietin mortality.

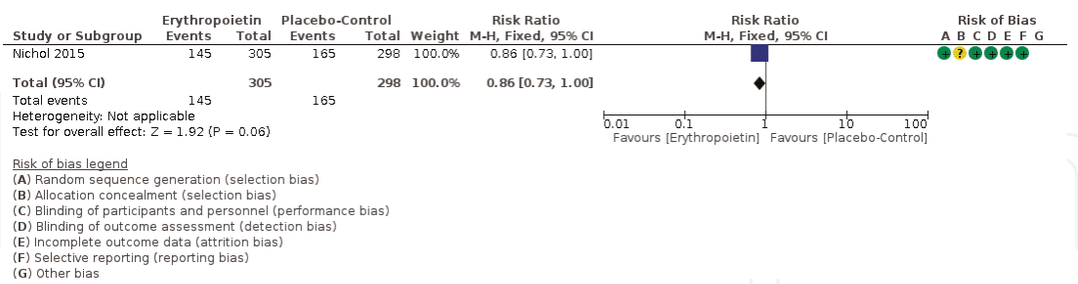

Figure 8.
Erythropoietin vascular side-effects.

trial [(p = 0.73; RR 0.93, 95% CI 0.62–1.39; participants = 603; studies = 1; I^2 = 0%) **Figure 9**], there was no side effect report in Aloizos et al. [51].

4.2.6 Magnesium sulfate and other magnesium salts

An updated review on magnesium, published in 2009 [23]; and no new studies been established in current review's search results after that timeline, the only study which was not mentioned in Vink et al. paper, was a pilot study on pediatric population with severe TBI, to maintain magnesium's feasibility and bio-availably for this population [52]. The common result of these studies, could be summarized

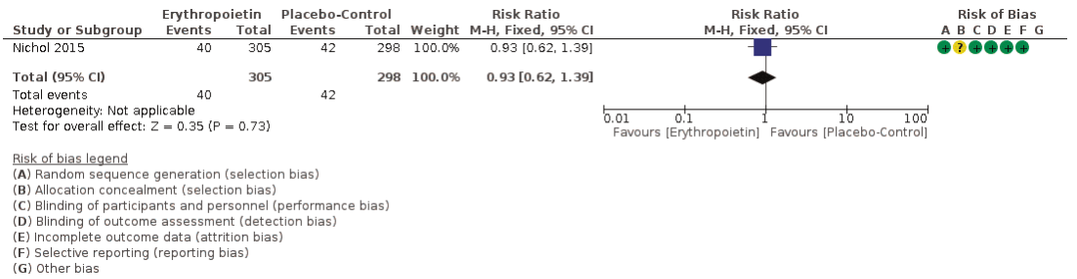

Figure 9.
Erythropoietin non-vascular side-effects.

as despite pre-clinical in-vivo studies of magnesium concentration in cerebrospinal fluid (CSF), that decline after acute TBI, and magnesium administration enhances its disposition in this field; no BBB feasibility seen in human studies for magnesium, and predicted mechanisms of actions for this intervention on human-beings are out of clinical evidence support [23, 52].

4.2.7 Cerebrolysin

There was a cohort-study by Wong et al. and a phase-II RCT by Chen et al. for cerebrolysin use in the search results [24, 53], also an ongoing huge multi-centric study held from third quarter of 2015 as well [54]. Cohort study, followed 42 patients with moderate to severe TBI, in 1:1 ratio, and report the outcomes in GOS scale after 6 months, which resulted in 67% good outcomes with cerebrolysin: placebo ratio of 19:14 in both study groups. The RCT reported cognitive outcomes with Mini-Mental Status Examination (MMSE) and Cognitive Abilities Screening Instrument (CASI) scales for mild TBI patients after 3 months that showed significant favorable outcome in intervention group [(p = 0.02; MD −13.40, 95% CI −24.87 to −1.93; participants = 32; studies = 1; I^2 = 0%) **Figure 10**].

4.2.8 Citicoline (CDP-choline) and other cholinergics

Articles related to citicoline intervention published from 1991–2014 [55–58]. Zafonte et al.'s study was a huge multicentric study a.k.a. COBRIT (citicoline brain injury treatment) and halted in its forth interim analysis due to non-significant outcome differences between placebo and intervention groups, but patients followed up to 180 days after injury, that 180 day's results are included in this review's analysis. Maldonado et al. and Shokouhi et al. studies didn't have placebo group, they were case-control studies, both included patients with severe or moderate acute TBI (216 and 58 patients respectively) [56, 57]. Leon-Carrion et al. study was a limited RCT of 10 patients for assessing neurocognitive effects of citicoline [55]. COBRIT planned to enroll 1292 patients, which halted in its forth interim analysis with 1213 patients randomized in two placebo and citicoline groups, the

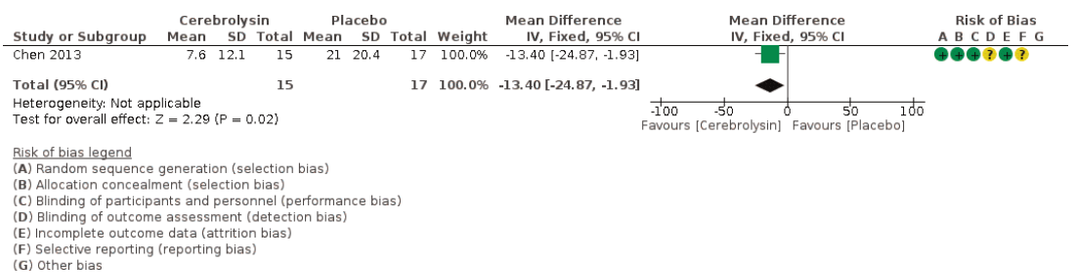

Figure 10.
Cognitive changes for cerebrolysin.

primary outcome assessment on day 90 of patients, was available for 996 cases, while 180-day outcome enrolled 902 cases [58].

In total, this meta-analysis included four studies with 1196 patients, which COBRIT study weighs about 75% of the analysis. The starting citicoline dose in studies was 2 g/day in Zafonte et al. and Shokouhi et al.'s trials, 1 g/day in Leon-Carrion et al.'s study, and 4 g/day in Maldonado et al.'s (that reduced to 3 g/day after day 3–4 of intervention and 2 g/day in case phlebitis would recognized).

Meta-analysis of outcomes showed no significant change in GOS outcome [(p = 0.76; RR 1.03, 95% CI 0.86–1.24; participants = 1128; studies = 2; I^2 = 71%) **Figure 11**], but significant favorable of neurocognitive changes in placebo-control group despite studies heterogeneity [(p < 0.00001; SMD 1.00, 95% CI 0.75–1.25; participants = 971; studies = 3) **Figure 12**]. However the comparison of COBRIT study's days-90 and 180 GOS outcomes, demonstrated improvements in day 180 outcomes [58]. Mortality and vegetative-state outcomes were analyzed together in studies, which only two studies (Maldonado et al. and Zafonte et al.) reported these outcomes with no significant difference [(p = 0.96; RR 0.98, 95% CI 0.51–1.86; participants = 1429; studies = 2; I^2 = 67%) **Figure 13**]. The side-effects of intervention at all has no significant difference between trial groups either [(p = 0.53; RR 1.03, 95% CI 0.94–1.12; participants = 1429; studies = 2; I^2 = 57%) **Figure 14**].

4.2.9 NeuroAid

There was no trial for NeuroAid use in TBI.

4.2.10 Cyclosporine A (CysA)

Search strategies results, brought five articles for this topic; and all were prospective clinical trials, Brophy et al., Empey et al., and Mazzeo et al. (in 2008) reported and analyzed Cyclosporine's concentration and safety dose for human use

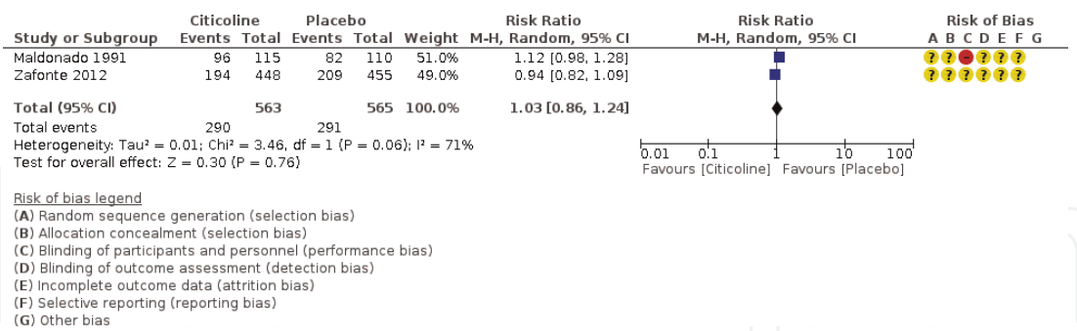

Figure 11.
Citicoline favorable outcome (GOS results).

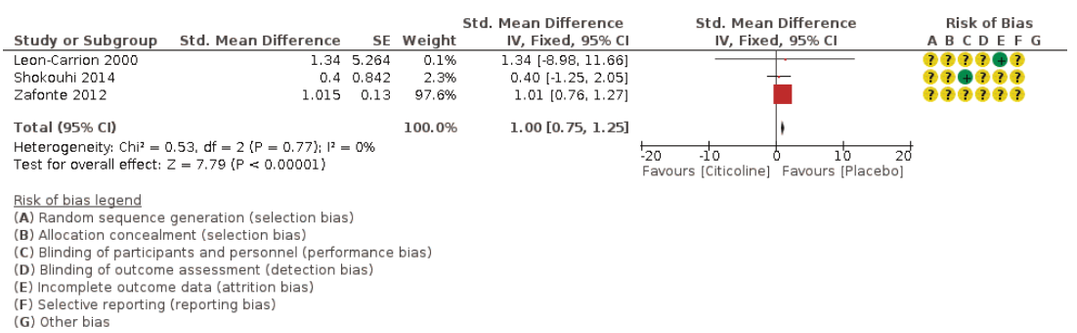

Figure 12.
Citicoline favorable outcome (at all).

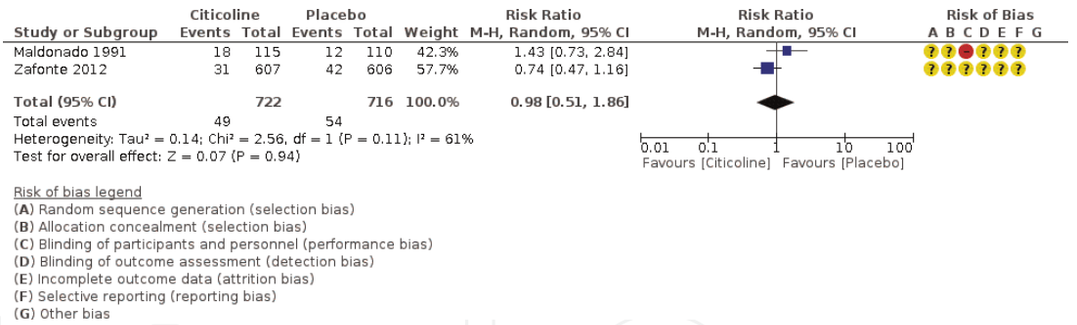

Figure 13.
Citicoline mortality.

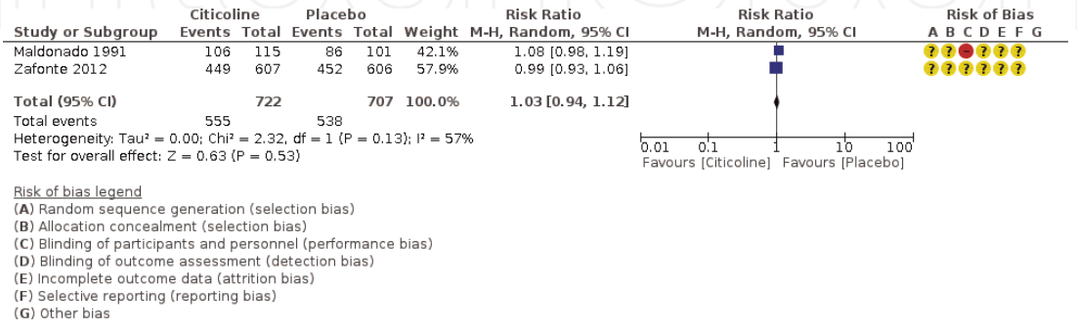

Figure 14.
Citicoline side-effects.

were [28, 59, 60]. The other two papers' population been analyzed at all were 89 patients [29, 61]. Cyclosporine's favorable GOS outcome analysis showed no significant difference between two interventional and placebo groups [(p = 0.83; RR 1.28, 95% CI 0.14–11.86; participants = 75; studies = 2; I^2 = 65%) **Figure 15**]; either there was no significant difference in mortalities [(p = 0.76; RR 1.17, 95% CI 0.443.12; participants = 89; studies = 2; I^2 = 0%) **Figure 16**] but CysA had significant effect on ICP control, and less ICP rise in comparison to placebo [(p = 0.01; RR 0.70, 95% CI 0.53–0.92; participants = 89; studies = 2; I^2 = 39%) **Figure 17**].

4.2.11 Rivastigmine

Three articles were related to this intervention in search results [30, 31, 62]. Silver et al. [31] was the continuation follow-up of Silver et al. [30] trial, which all placebo and rivastigmine group of 2006 study, got through rivastigmine intervention for 26 extra weeks, the results of this article, didn't differ significantly from the last report, so the 2009 study was excluded from the analysis; Tenovuo's study was

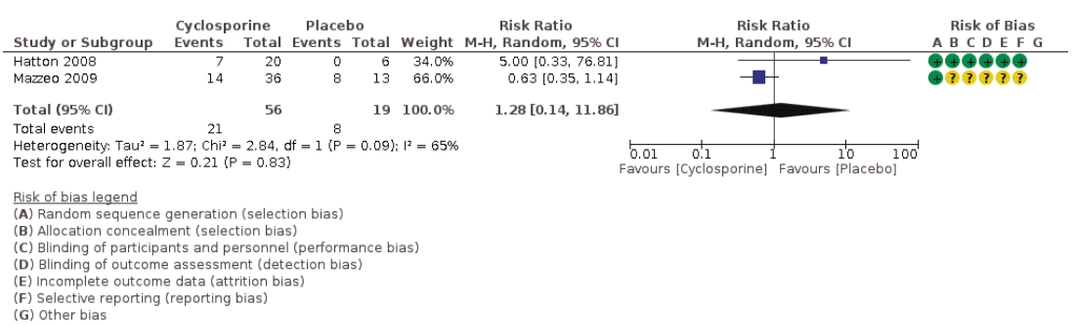

Figure 15.
Cyclosporine favorable outcome.

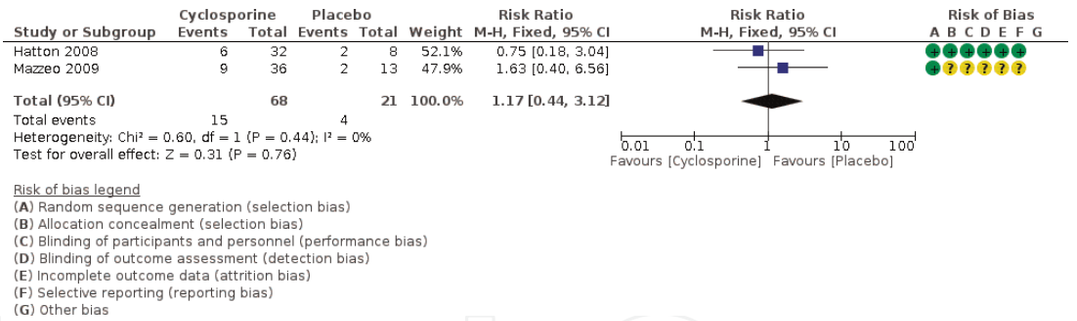

Figure 16.
Cyclosporine mortality.

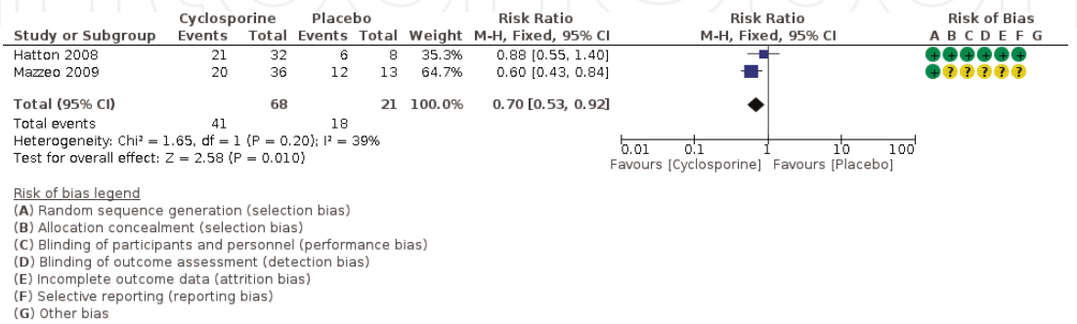

Figure 17.
Cyclosporine side effects (ICP rise).

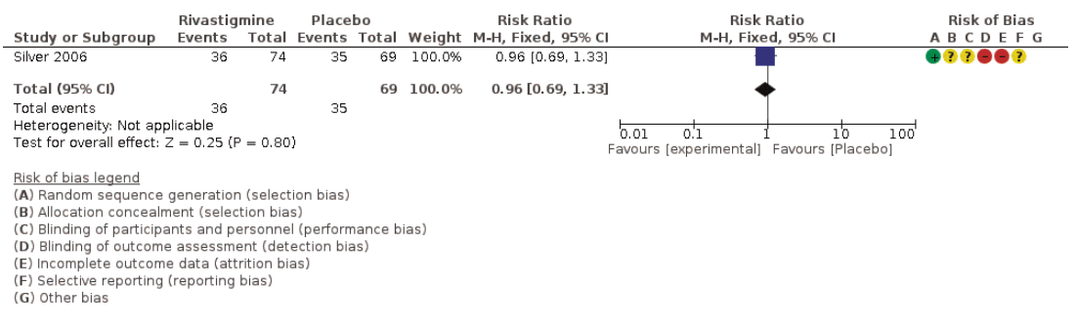

Figure 18.
Rivastigmine favorable outcome.

an out-patient clinic practice on 111 patients with three ChE-inh (Rivastigmine, Galantamine, and Donepezil), randomly assigned to patients by author, was excluded because of no placebo group, no blinding allocation statement and no obvious concealment reporting. Which all of these three articles lead results reporting to Silver et al. [30] trial, with 157 randomized patients in 77 placebo and 80 rivastigmine groups.

Silver et al. [30] study, has no mortality report in cases, but patients whom completed 12 weeks of trial time-line, were 70 in rivastigmine and 64 in placebo groups, also three patients in total lost to follow up (one in rivastigmine and two in placebo group); There was no significant difference for favorable outcome results of this intervention in comparison to placebo [(p = 0.80; RR 0.96, 95% CI 0.69–1.33; participants = 143; studies = 1; I^2 = 0%) **Figure 18**]. But authors stated that rivastigmine was efficient for more severe impaired patients in both 2006 and 2009 reports [30, 31]; it was analyzed as a sub-group analysis of 25% of patients and its raw results were not declared in the studies. Side-effect analysis show no meaningful difference too [(p = 0.74; RR 1.04, 95% CI 0.84–1.27; participants = 157; studies = 1; I^2 = 0%) **Figure 19**].

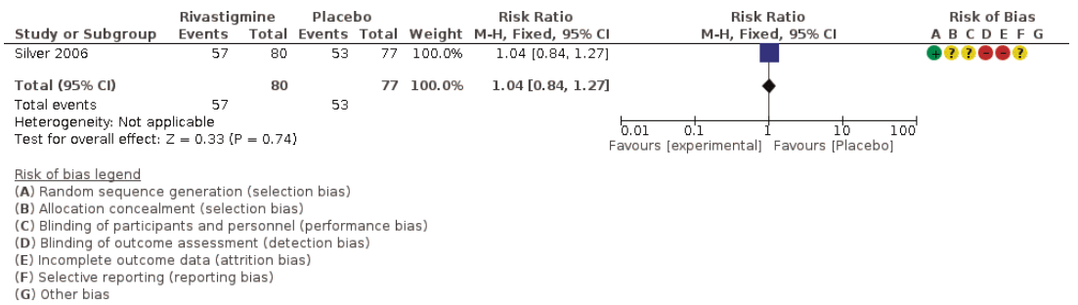

Figure 19.
Rivastigmine side effects.

4.2.12 Piracetam

Search results brought following three titles for this intervention "Clinical Evaluation of Nootropil (Piracetam) in Severe Craniocerebral Injuries," "Clinical trial of piracetam in disorders of consciousness due to head injury," and "A controlled clinical study piracetam V. Placebo in disorders of consciousness due to head injuries" but there was no achievement to their full-texts. However attempts to contact authors had no success too.

4.2.13 Miscellaneous findings

There were review-like studies and RCTs, further than these 12 categorized neuroprotectives, for TBI management, that a quick review of them proceeds in the following paragraphs

a. A 2013 "meta-analysis of treating acute traumatic brain injury with calcium channel blockers," of nine RCTs, showed slightly better outcome of placebo group, but it was not statistically significant (p = 0.52; RR 1.18, 95% CI 0.72–1.95; participants = 171; studies = 2; I2 = 52%), however there was no significant difference between intervention and placebo groups in mortalities (p = 0.44; RR 0.93, 95% CI 0.77–1.12; participants = 1337; studies = 5; I2 = 0%), nor adverse effects (p = 0.33; RR 1.11, 95% CI 0.90–1.37; participants = 1358; studies = 4; I2 = 0%) [63]. The former hypothesis of "The role of mitochondrial calcium uni-porter in neuroprotection in traumatic brain injury" may be disclaimed as a result of this meta-analysis [64].

b. A parallel study to COBRIT "Early trajectory of Psychiatric Symptoms after Traumatic Brain Injury: Relationship to patient and Injury Characteristic," show overall an improvement process of psychiatric characteristic of TBI patient over 180 days assessment, with better outcomes on days 30–90; better outcomes of female participants in comparison to males; not statistical significant but Hispanic's most and African-American's least improvement process in comparison to whites as the ethnic/race analysis' reference group [65].

- Better significant emotion recognition training outcome by the mean of 11 years after TBI in facial affect recognition better than participants of stories group in comparison to control group, showed impaired cognitive abilities improvement in moderate to severe TBI patients in "A randomized controlled trial of emotion recognition training after traumatic brain injury" [66]; however hypothetical testing of stories group to assess their ability to infer and label their feelings in given

scenarios, showed significant improvements. Patients responses to these emotional recognitions, was not favorable, as authors recommend further studies to instruct participants on how to response too [66].

- Hyperthermia after acute TBI, significantly results in unfavorable outcomes and mortality rates of especially severe head injured patients [67]; a Cochrane review of "Cooling for cerebral protection during brain surgery" didn't show significant result for this intervention [68], which might be due to different purposes of studies.

- And Finally a before-after clinical trial of 35 patients for "Effect of light music on physiological parameters of patients with traumatic brain injuries at intensive care units" using Dr. ArndStein's 70–80 metronome rhythmic melody, showed better significant physiologic outcomes in decreasing systolic and diastolic blood pressure, pulse rate, respiratory rate, arterial blood pressure and body temperature and increasing arterial oxygen saturation (<0.001); however pulse pressure decreasing was not significant [69].

4.2.14 Risk of bias in included studies

As a whole, "randomization part" of studies has a good assessment overall; however "allocation concealment" or "how blinding participants or personnel take place" didn't seem to be well reported. Finally RCTs reporting didn't accommodate well enough to CONSORT statement (i.e., this review study's tool for analyzing study reports). **Figures 20** and **21** are at a glance quick look assessment of risk of bias in included studies.

4.2.15 Effects of interventions

Overall, by the analysis of only phase-III studies results, no significant difference seen between neuroprotectives and placebo groups in favorable outcomes [(p = 0.30; RR 0.97, 95% CI 0.90–1.03; participants = 3560; studies = 4; I^2 = 0%) **Figure 22**]; or mortalities [(p = 0.51; RR 0.92, 95% CI 0.73–1.17; participants = 3876; studies = 4; I^2 = 52%) **Figure 23**].

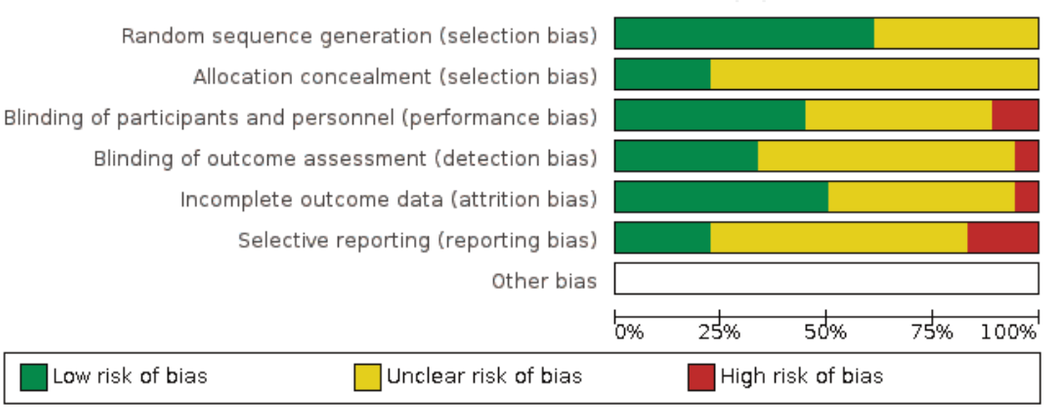

Figure 20.
Risk of biases graph: review author's judgments about each risk of bias item presented as percentages across all included studies.

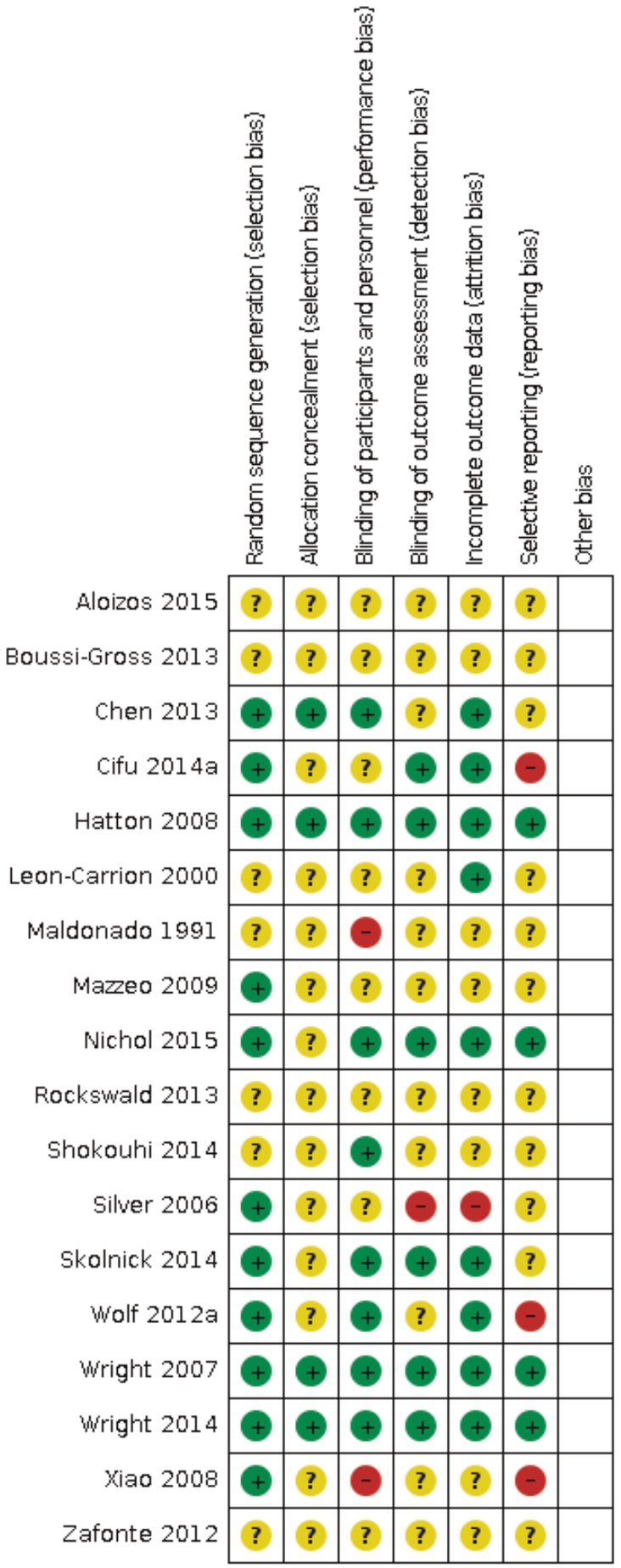

Figure 21.
Risk of biases summary: review author's judgments about each risk of bias item for each included study.

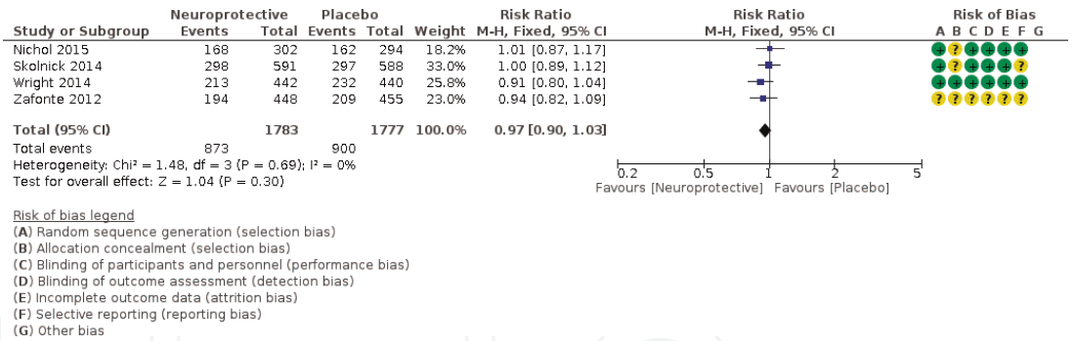

Figure 22.
Phase-III neuroprotectives favorable outcome.

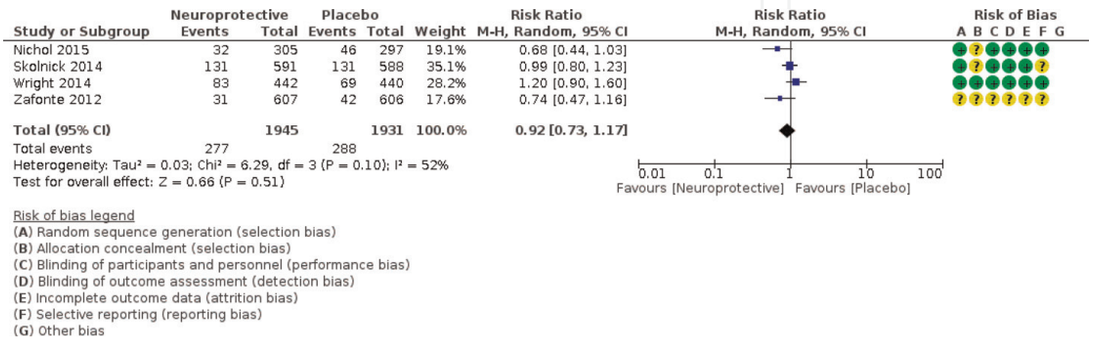

Figure 23.
Phase-III neuroprotectives mortality (CRASH 2005 not included).

5. Discussion

5.1 Summary of main results

5.1.1 Oxygen

Despite other trials of oxygen intervention in acute phase TBI, Rockswald et al. study's new design in combination of HBO_2/NBH, rather than solely attempt of each one results in better and significant outcomes [43]; it could be a new recommendation for future trials of acute phase TBI management, as its mortality report was the same as past trials, but with better GOS outcome [1, 43].

Boussi-Gross et al. study's improvement results in cognitive function of mild chronic TBI patients despite other DoD-/VA-related studies' results may be due to differences in civilian and service member populations of each study design, probable posttraumatic syndrome disorder (PTSD) symptoms of DoD/VA members, and different assessment tools; also, controversies of eye problem conditioning between Cifu et al. and Wolf et al. may resolve in a large group study with a common manifest of study objectives and participant evaluation [37, 38, 40–42].

In conclusion, there were lots of controversies between oxygen phase-II trials till now, but no multi-centric phase-III trial been conducted for this intervention, the one is strongly recommended also in a normal population and not just for DoD/VAs [41]. A Trial of HBO_2/NBH—(sham) control design may have most cost-beneficence than other kinds of solo intervention trials especially in acute phase TBI management [43]. Using oxygen (especially HBO_2) in chronic management of TBI has no enough evidences yet.

5.1.2 Corticosteroids

CRASH study's results that weigh about 95% of the Alderson's Cochrane review in "Corticosteroids for acute traumatic brain injury—last revised 2009," made the fact of increasing mortalities in TBI, by using corticosteroids [4]; no new trials found on steroids effect for TBI after these papers.

Current review's applicability on using corticosteroids for CNS acute traumas, leads to another Cochrane review of "Steroids for acute spinal cord injury—last revised 2012" [13]; however these conditions (TBI and SCI) may coincide (dual-diagnoses). So what are the practical recommendations for these situations?

According to Bracken's review "Methylprednisolone sodium succinate must be started within 8 hours of injury, using an initial bolus of 30 mg/kg by IV for 15 minutes followed 45 minutes later by a continuous infusion of 5.4 mg/kg/hour for 24 hours. Further improvement in motor function recovery has been shown to occur when the maintenance therapy is extended for 48 hours. This is particularly evident when the initial bolus dose could only be administered 3–8 hours after injury"; dosage and limited time of intervention for SCI patients, mentioned in the review by contemplate of situations with cohesion of TBI and SCI literally 16–59% [70], therefore challenging decision making on using corticosteroids (especially Methylprednisolone, as recommended in the review) on these conditions needs awareness of reviews results combination. It's suggested to use the recommended methylprednisolone protocol for dual-diagnose patients only in the initial bolus dose timing of 3–8 hours after acute injury, following therapy for only 48 hours; neither other corticosteroids nor extensive use of this protocol, are not suggested or acceptable for dual-diagnose patients management, also Nott et al. study brings hopes in cognitive behavior of dual-diagnosed ones [70], that discussed by social effects of condition in the study, this may persuade health-care practitioner and cost-benefit analyst about using this intervention for dual-diagnoses.

5.1.3 Progesterone

SYNAPSE and ProTECT-III trials results for progesterone, changed the former vision of this intervention's effect on TBI management, as CRASH trial did for corticosteroid in 2005.

Progesterones are gonadal steroids, and assume to have been more favorable in neurodegenerative disorders like multiple sclerosis (MS), Alzheimer disease (AD), and maybe TBI, i.e., neurodegenerative effects of microglia after injury and induced inflammatory response in whole body [14, 16, 71], as mentioned by Beyer [15].

Leucht et al. and Burns et al. studies results are good challenging statements for current visions of pharmaceutical interventions for major chronic disorders and central nervous system (CNS) injuries respectively [9, 12]. The pharmaceutical interventions failure in huge phase-III trials for TBI in the last decade (i.e., from CRASH 2005 to EPO-TBI 2015), even as smoothly penetration of progesterone through BBB to take its promising effects in pre-clinical studies [10, 11, 14, 15, 17, 18], made this statement from Wright et al. who designed and proceed three trials of progesterone use in TBI [10, 45, 47] "Despite these design strategies and extensive efforts, the trial did not confirm the efficacy of progesterone in patients with acute TBI. It is possible that the heterogeneity of the injury, confounding preexisting conditions, and characteristics of individual patients (e.g., resilience), which can be well controlled in animal models, play too large a role to overcome in human disease. Approaches are needed to reduce heterogeneity, but they come at the cost of more homogeneous pathological findings and decreased generalization of the results. Success at translating from bench to bedside may require new

paradigms, including innovative clinical-trial methods (e.g., adaptive designs and profiling of patients who have a response) in early-phase clinical trials to identify effective drug doses and timing (e.g., pre-hospital administration), the use of targeted outcomes based on the mechanism of injury, and rigorous preclinical multicentric trials in animals that better simulate subsequent human trials and make more accurate predictions regarding results." [10] "From Bench to Bed," "From Mice to Mind"; these statements declare incompatibility of basic studies with clinical trials; the basic science consortium approach, is one of good options for pharmaceutical intervention selection on human beings trials, it's on the way, as part of Combat Casualty Care Research Program-Operational Brain Trauma Therapy Consortium [11].

Concluding all these results together, may associate the future attempts on medicine to cellular-molecular field of bio-medicine in all of its era, as well as trauma management [9]. Review results should declare that using progesterone in the recommended I.V. doses has no significant beneficial effects than placebo; recommendation of using progesterone for pediatric patients in TBI insults [16], has no proof, as there is no structured RCT for that, and this age group's recovery of TBI effects, may naturally take place with controlling the damage by current guidelines. "Combination therapy of 17-Beta-E2 and Progesterone while applying a basis of Emulsion I.V. together with Omega-3 fatty acids, using high short-term dosages of treatments rather than normal long-term treatments" mentioned by Beyer as request of expertise-comment for his interests and experience since 1988 on Gonadal Steroids use for CNS problems [15] may present the clue for further researches in this field. Combination therapy of progesterone and vitamin D, especially in aged TBI patients [10, 14] is not proved in human cases, and beneficence of this combination recommended therapy, might be questioned for not significant efficacy of progesterone use in lately human phase-III RCTs; however another RCTs should hold for vitamin D use for TBI patients to verify this statement.

5.1.4 Monoaminergic agents

Cochrane review for this topic didn't include any articles, also there was no new studies in this review's search results too, and as they recommended in their article "in the absence of clear evidence of benefit from Neuroprotective drug use, there is an urgent need to explore other potential modulators of late outcome from TBI. The reported results of these studies require replication in larger studies, extended to other groups including more severely injured patients, and children" would be the clue of further researches and trials.

5.1.5 Erythropoietin (EPO)

The total analysis and results of this topic demonstrate that, it reduces mortality rates but no significant efficacy of EPO rather than placebo or control groups is noted; also EPO-TBI resulted in side-effects, which didn't report in other two trials [20, 21, 51], that might be due to EPO-TBI's higher EPO dose use (40,000 IU up to 3 doses) in comparison to 10,000 IU for 7 days of Aloizos et al. and 1000 IU in 6 doses during 2 weeks of Abrishamkar et al. There were side effects in placebo group of EPO-TBI trial too; that challenges this statement. Nearly significant better outcome of side-effects for EPO group in Nichol et al. EPO-TBI trial is far away from last expectations of EPO trials [21, 49] that confirms Leucht et al. statement on drugs complexity effect [12]. All three trials administered the intervention through subcutaneous (S.C.) route, as Abrishamkar et al. declared, despite LAB trials, it's

nearly impossible to gather Intra-Ventricular route for agent administration in edematous TBI brain [20].

Final conclusion on this topic, otherwise its prospective phase-III multi-centric placebo-controlled RCT, cannot obviously be presented, due to different dose of interventions between studies (i.e., more than recommended does 1000–30,000 IU in EPO-TBI trial [21, 51]; better outcomes in mortality-rate and side-effects reduction for intervention group; But overall, it showed better outcome in placebo group, which makes the clinical decision-making a challenge on using EPO for acute TBI. It should be recommended to conduct another prospective phase-III multi-centric placebo-controlled RCT with intervention dose of no more than 30,000 IU during EPO-administration to conduct better decision about choosing this intervention wisely for acute TBI assaults.

5.1.6 Magnesium sulfate and other magnesium salts

Magnesium beneficence for human beings through its CSF concentration didn't proved with the former trials, and Vink et al. reported the fact in 2009 [23]. Further trials on magnesium concentration in CSF may conducted via its administration through Intra Ventricular route, to find out its probable Neuroprotective effect, however it seems not to be successful [20].

5.1.7 Cerebrolysin

Limited evidences for this intervention's effect on TBI patients, also in different severities of TBI, mild TBI in RCT study and moderate to severe TBI in cohort study [24, 55], couldn't investigate its reliability for generalized use recommendation in TBIs; Cerebrolysin Asian Pacific Trial in Acute Brain Injury and Neurorecovery (CAPTAIN) results [54] is going to lead the future responsibilities and decisions to use this intervention in TBI situations.

5.1.8 Citicoline (CDP-choline) and other cholinergics

COBRIT study for citicoline seems to be like CRASH, SYNAPSE and ProTECT-III or EPO-TBI, as it was a huge multicentric placebo-control RCT of citicoline, its halt in forth interim analysis, may resulted to less participant of patients in follow-up process, but it was none of significantly difference between groups' analysis, overall assessment of outcomes didn't demonstrate any significant effect of citicoline favorable especially in GOS, yet in COBRIT study's assessment of GOS for day-90 and 180, improvements are slightly better but not significant at all (from $p = 0.97$ to $p = 0.43$), there is significant improvement of placebo-control group patients in neurocognitive state rather than intervention group. Yet neither mortality nor side-effects of intervention versus control groups were significant.

Maldonado et al. study was the more notable one after Zafonte et al. COBRIT in these search results; this study, Leon-Carrion et al. and Shokouhi et al. studies' beneficence in citicoline use for severe and moderate TBIs, questioned by COBRIT overall outcomes both in day-90 and 180 outcomes [55–58]. Also a significant better outcome change was obvious in mildly complicated cases on day-180 outcome in COBRIT study [58]. Heterogeneity of intervention doses and outcome assessments in included studies surrounded by Zafonte et al. Study's results; though current use of citicoline for TBI in acute or chronic phase, is no more recommended by the results of this review, however it may have neurocognitive beneficiaries for mild TBI, that decision of using this experiment on these conditions, belongs to attending physician's opinion and other assessments.

5.1.9 NeuroAid

Trials on Neuroaid for brain injury conditions mostly studied its effects on stroke brain injuries; none of current study's search results, related to Neuroaid use in TBI; that may suggest the clue for future trials.

5.1.10 Cyclosporine A (CysA)

Cyclosporine A's use may prevent ICP rise or reduce it, in comparison to placebo as this analysis showed. However there is no significant effect of its use in 6-month favorable outcomes or mortality rates. Also cohort study groups of Hatton et al. and other drug concentration studies confirm that best blood and cerebrospinal fluid (CSF) CysA depositions resulted from its high doses and fortunately the wide therapeutic window [28, 59–61]. Both of the included studies have a 5 mg/kg intervention on their design protocols, also Hatton et al. recommended a 2.5 mg/kg bolus dose in 2 hours of TBI insult following by 5 mg/kg/day for 72 hours, as optimal dosing strategy for further clinical trials study design. As there would be a huge multi-centric, prospective, phase-III RCT for CysA after National Institute of Health (NIH) proves its proposal [29]; that might bring future evidences on using this intervention for TBI (especially acute) management.

5.1.11 Rivastigmine

Rivastigmine and other ChE-inh use for TBI, mostly known for their cognitive behavioral effects, and their trials take part in chronic TBI managements, Tenovuo's study didn't show a significant difference between three drugs that patients assigned to use, but mostly preferred Galantamine for its fewer side effects [62]. Silver et al. (both 2006 and 2009 studies) with 157 patients and better study design in comparison to Tenovuo's, didn't show significant difference of rivastigmine and placebo groups at all, but in severe impaired patients. These results support the need of more RCTs especially multi-centric phase-III RCTs of rivastigmine and other ChE-inh for chronic TBI management in severe impaired patients, the recommended protocol as Silver et al. Stated, is to start with 3 mg of rivastigmine/day and slowly increase to maximum dose of 12 mg/day if the previous dose was well tolerated for at least 4 weeks. Routine use of rivastigmine for chronic TBI management is not recommended, as it has no significant effect for patients rather than placebo, as current evidences declared.

5.1.12 Piracetam

There were studies for this intervention but no achievement to their full-texts, it may be one of this review's reporting biases, which no clinical judgment may presented for this intervention.

5.1.13 Miscellaneous findings

Following statements are recommendations for "Miscellaneous Findings" section of "Results" section of the study:

- Improvement in psychiatric assessments of TBI patient, after assault differ between individuals, there should be supportive psychological first aid (PFA) tools for primary survivors of the assault; a Johns Hopkins University's course of PFA-RAPID which stands for Rapport and Reflective Listening, Assessment

of Needs, Prioritization, Intervention, Disposition; is available at https://www.coursera.org/course/psychfirstaid to triage and primary effective intervene of health-care providers for trauma assaults survivors, as further than the insult, sub-acute complications during recovery of patients, especially in two-third of severe impaired TBI patients [72], may have affects on their family's life too.

- Cerebral and body cooling for acute TBI impaired patients, may have better outcomes in patients survival and reducing mortality rates, due to significant unfavorable outcomes and mortality rates of high fevered patients after acute TBI in Li et al. study; a strong evidence of phase-III multi-centric international RCT, needed to prove this statement.

- Music-therapy use for TBI patient, seem to have better outcomes in physiologic parameters, however other double-blinded RCTs need to prove this statement. However Maleki et al. study's aim was not to assess participants outcomes; as well actual efficacy of this intervention on patients outcomes, might took under survey too [9, 73, 74].

5.2 Overall completeness and applicability of evidence

All of RCTs checked with CONSORT 2010 checklist; the applicability of this tool for further analysis of probable biases from participant randomization to outcome report used on each of the included studies as well.

5.3 Potential biases in the review process

Primary database search strategy, didn't consist interventions as search keywords separately, the consultation with a medical librarian, persuade authors to revise the strategy with search of Piracetam, NeuroAid and Citicoline (as commonly used Neuroprotectives in their tertiary center, and for meta-analysis purpose of these interventions), the re-run search strategy added few (about 7–10) records in each database search, that skim review on their title and abstracts (duplicated records, assessed with Zotero reference manager software for exclusion), didn't show significant change of eligible studies, and further search on all interventions as solo keywords, didn't take place. Current meta-analyses based on second search strategy results. This may be a selection bias of this study and future reviews should be aware of this bias; another probable bias in this review was in reporting outcomes and mortalities analyses; Authors decide to report GOS or GOS-E outcomes analyses in two groups: (1) favorable outcome, which consists of good outcome and mild disability (GOS 4,5 and GOS-E 5-8) outcome; and (2) mortalities, that reported vegetative state and mortalities analysis (GOS 1,2 and GOS-E 1,2). Some of the articles, reported severe disability, vegetative-state and mortality outcomes together; if it was possible to get special reports on outcomes, analyses get through them, but if not, they'd been analyzed as the original article's authors decision.

5.4 Agreements and disagreements with other studies or reviews

This review was a brand-new in interventions analyses for TBI (mostly acute) management; other previous reviews based on significant intervention's effect analysis; some parts of this review used the former reviews or meta-analyses results conducting new one, are referred through the text.

5.5 Final pluralization

Overall conclusion of these results and outcome findings of neuroprotective agents for traumatic brain injury management could be summarized as follows:

a. Oxygen using for acute management of TBI to reduce mortality rates is obvious, however no significant change seen in favorable outcomes, if a setting has HBO_2 resource available, combined use of HBO_2/NBH, may have better patient outcomes than using HBO_2 or NBH solely; recommended approach for this facility is "combined HBO2/NBH treatment, which consisted of 100% FiO_2 delivered for 60 minutes at 1.5 ATA followed by 3 hours at 1.0 ATA" [43]; also there is no significant evidence for using HBO_2 in chronic TBI management.

b. Corticosteroid use in solo acute TBI management is prohibited, as its increased risk of mortalities; in dual-diagnosed patients (TBI and SCI together), corticosteroid use, should be obtained by this protocol [13]:

    i. patient came through 2–3 hours after assault (if longer, should not be obtained)

    ii. only methylprednisolone (other corticosteroids, has no beneficent effect in SCI management) with following protocol should be administered through IV route:

        - Bolus dose: 30 mg/kg in 15 minutes,

        - Following drip of: 5.4 mg/kg/day for the next 24–48 hours.

c. Current routine use of citicoline in acute TBI is no more supported, while no significant difference in comparison to placebo been reported. Citicoline use for managing neurocognitive conditions of chronic TBI, depends on attended physician's evaluation of patient's condition and local setting's evidence based medicine (EBM) community's decision. Rather its probable benefice in mild TBI patients, it's not recommended for all severity of TBI, while significant improvements seen in placebo group.

d. Using of Cyclosporine A for ICP control, depends on the setting's available resources, and attending physician's point of view, there is no other significant difference for its favorable outcome in comparison to placebo. it should be recommend to administer through IV route by following protocol in acute TBI management [61]:

    i. Bolus dose: 2.5 mg/kg in 2 hours,

    ii. Following drip of: 5 mg/kg/day for the next 72 hours.

e. Rivastigmine use for chronic TBI management of neurocognitive conditions, had some beneficence in severe impaired participants through phase-II trials of 3 mg/day and slowly increasing to 12 mg/day by adding 1.5 mg/day to previous dose if tolerated for 4 weeks of last dose [30].

f. Other neuroprotective agents use for acute or chronic management of TBI, has no field of support yet.

6. Conclusions

6.1 Recommendations for practice

To use oxygen in acute management of TBI in order to reduce mortality rates seems to be obvious, however no significant change seen in favorable outcomes; corticosteroid use in solo acute TBI management is prohibited, as it increases risk of mortalities, however in dual-diagnosed patients (TBI & SCI together), corticosteroid use, should be obtained by a protocol introduced by Bracken et al. Current routine use of citicoline in acute TBI is no more supported, while no significant difference in comparison to placebo been reported. Cyclosporine A usage for ICP control, depends on the available resources, and attending physician's point of view; Rivastigmine use for chronic TBI management of neurocognitive conditions, had some beneficence in severe impaired participants. However other Neuroprotective agents use for acute or chronic management of TBI, has no field of support yet and they needed more researches and trials.

6.2 Recommendations for research

Lastly phase-III RCTs for TBI management, change the former evidences of Neuroprotective agents use (i.e., CRASH 2005 for corticosteroid [4], COBRIT 2012 for citicoline [58]. SYNAPSE 2014 [11] and ProTECT 2014 [10] for Progesterone and EPO-TBI 2015 for erythropoietin [21]; despite current process of phase-I to phase-III (IV) new drug evaluation to use in human-beings, it should be recommended to skip phase-II trials for TBI related studies; heterogeneity of the condition, make its accurate interpretation so difficult in restricted single-centered phase-II trials. Scheduling large double (or more)-blinded huge multi-centric international phase-III RCTs, including low-income countries too as recommended by Menon in "Unique challenges in clinical trials in traumatic brain injury" [75], with acceptable design of interim analyses for number needed to harm (NNH) and number needed to treat (NNT) at regular checkpoints, seem to have more accuracy and cost-beneficent effects than current known processes. There was no strong-evidenced well-designed trials for these interventions:

- Combined therapy of HBO_2/NBH
- Monoaminergics;
- "High-dose, short-time administration of progesterone with 17-Beta-E2 in emulsion of Omega-3," as an expert advice for future studies [15] rather than SYNAPSE and ProTECT results;
- Administering magnesium solutions via Intra-Ventricular or other achievable routes in TBI patients for rising its concentration in TBI patient's CSF;
- Rivastigmine use for chronic management of severe impaired neurocognitive conditions;
- Cerebral or body cooling, especially in severely impaired patients of acute TBI assault.

Also a Cerebrolysin phase-III trial is in the ongoing-list of current study [54]. And despite NeuroAid's trials for stroke injured brain, there was no trial (even phase-II) of this intervention for TBI.

Cellular-molecular experiences in CNS conditions, has not been provided acceptable outcomes for TBI to date, but as a recommendation of an expert "there is potential for TBI" as "mirror pathophysiology of some of the other conditions," despite "the lack of sensitive outcome measures" there is hope to "promote at least some improvement in recovery of function via immunomodulation and promoting plasticity" [9].

It's also recommended for RCT authors to use CONSORT-assessment guidelines in their study designs and paper reports; and report clinical outcomes of mild, moderate and severe suffered acute TBI patients in separate subgroup analyses, which an eight-pointed GOS-E reporting scale is preferred to five-pointed GOS one [75]; till better outcome assessment tool been developed; however studies on hypotheses of drugs concentration in serum, or assessing physiological parameters of patients; resulted in no more significant outcome of TBI patients in large phase-III studies.

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Conflict of interest

This chapter is the reporting result of a GP graduation thesis from Tabriz University of Medical Sciences, which was defended on June 2016 under thesis number 92/1-1/6.

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References

[1] Bennett MH, Trytko B, Jonker B. Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. Cochrane Database of Systematic Reviews. 2012. [Internet]. [cited 2015 Dec 27];12. Available from: http://dev.biologists.org/content/3/4/326.short

[2] Roberts I, Schierhout G. Hyperventilation therapy for acute traumatic brain injury. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 1997. [Internet]. [cited 2015 Dec 26]. Available from: http://doi.wiley.com/10.1002/14651858.CD000566

[3] Thompson K, Pohlmann-Eden B, Campbell Leslie A, Abel H. Pharmacological treatments for preventing epilepsy following traumatic head injury (Review). Cochrane Database of Systematic Reviews. 2015. [Internet]. [cited 2015 Dec 26];8. Available from: http://journals.lww.com/ccmjournal/Abstract/2010/05000/Long_term_mortality_and_quality_of_life_in_sepsis_.6.aspx

[4] Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2005. [Internet]. [cited 2015 Dec 26]. Available from: http://doi.wiley.com/10.1002/14651858.CD000196.pub2

[5] Ma J, Huang S, Qin S, You C. Progesterone for acute traumatic brain injury. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2012. [Internet]. [cited 2015 Dec 26]. Available from: http://doi.wiley.com/10.1002/14651858.CD008409.pub3

[6] Sahuquillo J. Decompressive craniectomy for the treatment of refractory high intracranial pressure in traumatic brain injury. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006. [Internet]. [cited 2015 Dec 26]. Available from: http://doi.wiley.com/10.1002/14651858.CD003983.pub2

[7] National Institute of Neurological Disorders and Stroke. National Institute of Health - Traumatic Brain Injury. Traumatic Brain Injury; 2012

[8] MeSH. Neuroprotective Agents. Internet Based Definitions: NCBI. 1995. Available from: http://www.ncbi.nlm.nih.gov/mesh/68018696

[9] Burns TC, Verfaillie CM. From mice to mind: Strategies and progress in translating neuroregeneration. European Journal of Pharmacology. 2015;**759**:90-100

[10] Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, Frankel M, et al. Very early administration of progesterone for acute traumatic brain injury. The New England Journal of Medicine. 2014;**371**(26):2457-2466

[11] Skolnick BE, Maas AI, Narayan RK, van der Hoop RG, MacAllister T, Ward JD, et al. A clinical trial of progesterone for severe traumatic brain injury. The New England Journal of Medicine. 2014; **371**(26):2467-2476

[12] Leucht S, Helfer B, Gartlehner G, Davis JM. How effective are common medications—A perspective based on meta-analyses of major drugs. BioMed Centeral Ltd—BMC Medicine. 2015; **13**(1):253

[13] Bracken MB. Steroids for acute spinal cord injury. Cochrane Database of Systematic Reviews. 2002. [Internet]. [cited 2015 Dec 26];3(3). Available

from: http://info.onlinelibrary.wiley.com/userfiles/ccoch/file/CD001046.pdf

[14] Atif F, Sayeed I, Ishrat T, Stein DG. Progesterone with vitamin D affords better neuroprotection against excitotoxicity in cultured cortical neurons than progesterone alone. Molecular Medicine. 2009;**15**(9–10):328

[15] Hoffmann S, Beyer C. Gonadal steroid hormones as therapeutic tools for brain trauma: The time is ripe for more courageous clinical trials to get into emergency medicine. The Journal of Steroid Biochemistry and Molecular Biology. 2015;**146**:1-2

[16] Robertson CL, Fidan E, Stanley RM, Noje C, Bayir H. Progesterone for neuroprotection in pediatric traumatic brain injury. Pediatric Critical Care Medicine. 2015;**16**(3):236-244

[17] Kelley BG, Mermelstein PG. Progesterone blocks multiple routes of ion flux. Molecular and Cellular Neurosciences. 2011;**48**(2):137-141

[18] Luoma JI, Kelley BG, Mermelstein PG. Progesterone inhibition of voltage-gated calcium channels is a potential neuroprotective mechanism against excitotoxicity. Steroids. 2011. [Internet]. [cited 2015 Dec 26]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S0039128X11000535

[19] Forsyth RJ, Jayamoni B, Paine TC, Mascarenhas S. Monoaminergic agonists for acute traumatic brain injury. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006. [Internet]. [cited 2015 Dec 26]. Available from: http://doi.wiley.com/10.1002/14651858.CD003984.pub2

[20] Abrishamkar S, Safavi M, Honarmand A. Effect of erythropoietin on Glasgow coma scale and Glasgow outcome Sale in patient with diffuse axonal injury. Journal of Research in Medical Sciences. 2012;**17**(1):51

[21] Nichol A, French C, Little L, Haddad S, Presneill J, Arabi Y, et al. Erythropoietin in traumatic brain injury (EPO-TBI): A double-blind randomised controlled trial. The Lancet. 2015;**386**(10012):2499-2506

[22] Presneill J, Little L, Nichol A, French C, Cooper D, Haddad S, et al. Statistical analysis plan for the erythropoietin in traumatic brain injury trial: A randomised controlled trial of erythropoietin versus placebo in moderate and severe traumatic brain injury. Trials. 2014;**15**(1):501

[23] Vink R, Cook NL, van den Heuvel C. Magnesium in acute and chronic brain injury: An update. Magnesium Research. 2009;**22**(3):158-162

[24] Wong GKC, Zhu XL, Poon WS. Beneficial effect of cerebrolysin on moderate and severe head injury patients: Result of a cohort study. In: Intracranial Pressure and Brain Monitoring XII. Springer; 2005. [Internet]. [cited 2015 Dec 26]. p. 59–60. Available from: http://link.springer.com/chapter/10.1007/3-211-32318-X_13

[25] Tan HB, Wasiak J, Rosenfeld JV, O'Donohoe TJ, Gruen RL. Citicoline (CDP-choline) for traumatic brain injury. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2014. [Internet]. [cited 2015 Dec 26]. Available from: http://doi.wiley.com/10.1002/14651858.CD011217

[26] Chen C, Venketasubramanian N, Gan RN, Lambert C, Picard D, Chan BP, et al. Danqi Piantang Jiaonang (DJ), a traditional Chinese medicine, in poststroke recovery. Stroke. 2009;**40**(3):859-863

[27] Heurteaux C, Gandin C, Borsotto M, Widmann C, Brau F, Lhuillier M, et al. Neuroprotective and neuroproliferative activities of NeuroAid (MLC601,

MLC901), a Chinese medicine, in vitro and in vivo. Neuropharmacology. 2010; **58**(7):987-1001

[28] Mazzeo AT, Alves ÓL, Gilman CB, Hayes RL, Tolias C, Niki Kunene K, et al. Brain metabolic and hemodynamic effects of cyclosporin a after human severe traumatic brain injury: A microdialysis study. Acta Neurochirurgica. 2008;**150**(10): 1019-1031

[29] Mazzeo AT, Brophy GM, Gilman CB, Alves ÓL, Robles JR, Hayes RL, et al. Safety and tolerability of cyclosporin a in severe traumatic brain injury patients: Results from a prospective randomized trial. Journal of Neurotrauma. 2009;**26**(12):2195-2206

[30] Silver JM, Koumaras B, Chen M, Mirski D, Potkin SG, Reyes P, et al. Effects of rivastigmine on cognitive function in patients with traumatic brain injury. Neurology. 2006;**67**(5): 748-755

[31] Silver JM, Koumaras B, Meng X, Potkin SG, Reyes PF, Harvey PD, et al. Long-term effects of rivastigmine capsules in patients with traumatic brain injury. Brain Injury. 2009;**23**(2): 123-132

[32] Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. 2011. Available from: http://handbook.cochrane.org

[33] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. British Medical Journal. 2003;**327**(7414):557

[34] Rognås L, Hansen TM, Kirkegaard H, Tønnesen E. Anaesthesiologist-provided prehospital airway management in patients with traumatic brain injury: An observational study. European Journal of Emergency Medicine. 2014;**21**(6):418-423

[35] Bell MJ, Adelson PD, Hutchison JS, Kochanek PM, Tasker RC, Vavilala MS, et al. Differences in medical therapy goals for children with severe traumatic brain injury—An international study. Pediatric Critical Care Medicine. 2013; **14**(8):811-818

[36] Huizenga JE, Zink BJ, Maio RF, Hill EM. Guidelines for the management of severe head injury: Are emergency physicians following them? Academic Emergency Medicine. 2002;**9**(8): 806-812

[37] Cifu DX, Hart BB, West SL, Walker W, Carne W. The effect of hyperbaric oxygen on persistent postconcussion symptoms. The Journal of Head Trauma Rehabilitation. 2014;**29**(1):11-20

[38] Cifu DX, Walker WC, West SL, Hart BB, Franke LM, Sima A, et al. Hyperbaric oxygen for blast-related postconcussion syndrome: Three-month outcomes: HBO_2 RCT for PCS outcomes. Annals of Neurology. 2014;**75**(2): 277-286

[39] Cifu DX, Hoke KW, Wetzel PA, Wares JR, Gitchel G, Carne W. Effects of hyperbaric oxygen on eye tracking abnormalities in males after mild traumatic brain injury. Journal of Rehabilitation Research and Development. 2014;(7):51, 1047-1056

[40] Wolf G, Cifu D, Baugh L, Carne W, Profenna L. The effect of hyperbaric oxygen on symptoms after mild traumatic brain injury. Journal of Neurotrauma. 2012;**29**(17):2606-2612

[41] Wolf EG, Prye J, Michaelson R, Brower G, Profenna L, Boneta O. Hyperbaric side effects in a traumatic brain injury randomized clinical trial. [Internet]. DTIC Document; 2012 [cited 2015 Dec 26]. Available from: http://oai.dtic.mil/oai/oai?verb=getRecord&metadataPrefix=html&identifier=ADA611409

[42] Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury-randomized prospective trial. Ai J, editor. PLoS One. 2013;**8**(11):e79995

[43] Rockswold SB, Gaylan L, Rockswold DA, Jiannong L. A prospective, randomized phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. Journal of Neurosurgery. 2013; **118**(6):1317-1328

[44] Shakeri M, Boustani MR, Pak N, Panahi F, Salehpour F, Lotfinia I, et al. Effect of progesterone administration on prognosis of patients with diffuse axonal injury due to severe head trauma. Clinical Neurology and Neurosurgery. 2013;**115**(10):2019-2022

[45] Wright DW, Kellermann AL, Hertzberg VS, Clark PL, Frankel M, Goldstein FC, et al. ProTECT: A randomized clinical trial of progesterone for acute traumatic brain injury. Annals of Emergency Medicine. 2007;**49**(4): 391-402.e2

[46] Xiao G, Wei J, Yan W, Wang W, Lu Z. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: A randomized controlled trial. Critical Care. 2008;**12**(2):R61

[47] Wright DW, Ritchie JC, Mullins RE, Kellermann AL, Denson DD. Steady-state serum concentrations of progesterone following continuous intravenous infusion in patients with acute moderate to severe traumatic brain injury. Journal of Clinical Pharmacology. 2005;**45**(6):640-648

[48] Xiao G, Wei J, Wu Z, Wang W, Jiang Q, Cheng J, et al. Clinical study on the therapeutic effects and mechanism of progesterone in the treatment for acute severe head injury. Zhonghua Wai Ke Za Zhi. 2007;**45**(2):106-108

[49] Mammis A, McIntosh TK, Maniker AH. Erythropoietin as a neuroprotective agent in traumatic brain injury. Surgical Neurology. 2009;**71**(5):527-531

[50] Talving P, Lustenberger T, Kobayashi L, Inaba K, Barmparas G, Schnüriger B, et al. Erythropoiesis stimulating agent administration improves survival after severe traumatic brain injury: A matched case control study. Annals of Surgery. 2010;**251**(1): 1-4

[51] Aloizos S, Evodia E, Gourgiotis S, Isaia E, Seretis C, Baltopoulos G. Neuroprotective effects of erythropoietin in patients with severe closed brain injury. Turkish Neurosurgery. 2015. [Internet]. [cited 2015 Dec 26]; Available from: http://www.turkishneurosurgery.org.tr/summary_en_doi.php3?doi=10.5137/1019-5149.JTN.9685-14.4

[52] Natale JE, Guerguerian A-M, Joseph JG, McCarter R, Shao C, Slomine B, et al. Pilot study to determine the hemodynamic safety and feasibility of magnesium sulfate infusion in children with severe traumatic brain injury. Pediatric Critical Care Medicine. 2007; **8**(1):1-9

[53] Chen C-C, Wei S-T, Tsaia S-C, Chen X-X, Cho D-Y. Cerebrolysin enhances cognitive recovery of mild traumatic brain injury patients: Double-blind, placebo-controlled, randomized study. British Journal of Neurosurgery. 2013; **27**(6):803-807

[54] Poon W, Vos P, Muresanu D, Vester J, von Wild K, Hömberg V, et al. Cerebrolysin Asian Pacific trial in acute brain injury and neurorecovery: Design and methods. Journal of Neurotrauma. 2015;**32**(8):571-580

[55] Leon-Carrion J, Dominguez-Roldan J, Murillo-Cabezas F, del Rosario D, Munoz-Sanchez M. The role of citicholine in neuropsychological training after traumatic brain injury. Neuropsychological Rehabilitation. 1999;**14**(1):33-40

[56] Maldonado V, Perez J, Escario J. Effects of CDP-choline on the recovery of patients with head injury. Journal of the Neurological Sciences. 1991;**103**: 15-18

[57] Shokouhi G, Ghorbani Haghjoo A, Sattarnezhad N, Asghari M, Sattarnezhad A, Asghari A, et al. Effects of citicoline on level of consciousness, serum level of fetuin-A and matrix Gla-protein (MGP) in trauma patients with diffuse axonal injury (DAI) and GCS ≤ 8. Turkish Journal of Trauma and Emergency. 2014;**20**(6):410-416

[58] Zafonte RD, Bagiella E, Ansel B, Novack TA, Friedewald WT, Hesdorffer DC, et al. Effect of citicoline on functional and cognitive status among patients with traumatic brain injury: Citicoline brain injury treatment trial (COBRIT). Journal of the American Medical Association. 2012;**308**(19): 1993-2000

[59] Brophy GM, Mazzeo AT, Brar S, Alves OL, Bunnell K, Gilman C, et al. Exposure of Cyclosporin A in whole blood, cerebral spinal fluid, and brain extracellular fluid dialysate in adults with traumatic brain injury. Journal of Neurotrauma. 2013;**30**(17):1484-1489

[60] Empey PE, McNamara PJ, Young B, Rosbolt MB, Hatton J. Cyclosporin A disposition following acute traumatic brain injury. Journal of Neurotrauma. 2006;**23**(1):109-116

[61] Hatton J, Rosbolt B, Empey P, Kryscio R, Young B. Dosing and safety of cyclosporine in patients with severe brain injury: Clinical article. Journal of Neurosurgery. 2008;**109**(4):699-707

[62] Tenovuo O. Central acetylcholinesterase inhibitors in the treatment of chronic traumatic brain injury—Clinical experience in 111 patients. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2005;**29**(1):61-67

[63] Xu G-Z, Wang M-D, Liu K-G, Bai Y-A, Wu W, Li W. A meta-analysis of treating acute traumatic brain injury with calcium channel blockers. Brain Research Bulletin. 2013; **99**:41-47

[64] Cheng G, Fu L, Zhang H, Wang Y, Zhang L, Zhang J. The role of mitochondrial calcium uniporter in neuroprotection in traumatic brain injury. Medical Hypotheses. 2013;**80**(2): 115-117

[65] Hart T, Benn EKT, Bagiella E, Arenth P, Dikmen S, Hesdorffer DC, et al. Early trajectory of psychiatric symptoms after traumatic brain injury: Relationship to patient and injury characteristics. Journal of Neurotrauma. 2014;**31**(7):610-617

[66] Neumann D, Babbage DR, Zupan B, Willer B. A randomized controlled trial of emotion recognition training after traumatic brain injury. The Journal of Head Trauma Rehabilitation. 2015; **30**(3):E12-E23

[67] Li J, Jiang J. Chinese head trauma data bank: Effect of hyperthermia on the outcome of acute head trauma patients. Journal of Neurotrauma. 2012;**29**(1): 96-100

[68] Galvin IM, Levy R, Boyd JG, Day AG, Wallace MC. Cooling for cerebral protection during brain surgery. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2015. [cited 2015 Dec 26]. Available from: http://doi.wiley.com/10.1002/14651858.CD006638.pub3

[69] Maleki M, Ghaderi M, Ashktorab T, Jabbari-Noghabi H, Zadehmohammadi A. Effect of light music on physiological parameters of patients with traumatic brain injuries at intensive care unit. Ofogh-E-Danesh. 2011;**18**(1):66-75

[70] Nott M, Baguley I, Heriseanu R, Weber G, Middleton J, Meares S, et al. Effects of concomitant spinal cord injury and brain injury on medical and functional outcomes and community participation. Topics in Spinal Cord Injury Rehabilitation. 2014;**20**(3): 225-235

[71] Stein DG, Cekic MM. Progesterone and vitamin D hormone as a biologic treatment of traumatic brain injury in the aged. PM & R Journal. 2011;**3**(6): S100-S110

[72] Godbolt AK, Stenberg M, Jakobsson J, Sorjonen K, Krakau K, Stålnacke B-M, et al. Subacute complications during recovery from severe traumatic brain injury: Frequency and associations with outcome. BMJ Open. 2015;**5**(4):e007208

[73] Cinotti R, Ichai C, Orban J, Kalfon P, Feuillet F, Roquilly A, et al. Effects of tight computerized glucose control on neurological outcome in severely brain injured patients a multicenter sub-group analysis of the randomized-controlled open-label CGAO-REA study. Critical Care (London, England). 2014;**18**(5): 498

[74] Rhind SG, Crnko NT, Baker AJ, Morrison LJ, Shek PN, Scarpelini S, et al. Prehospital resuscitation with hypertonic saline-dextran modulates inflammatory, coagulation and endothelial activation marker profiles in severe traumatic brain injured patients. Journal of Neuroinflammation. 2010; **7**(5):1-17

[75] Menon DK. Unique challenges in clinical trials in traumatic brain injury. Critical Care Medicine. 2009;**37** (Supplement):S129-S135