Therapeutic Strategies in Traumatic Intracranial Hemorrhage and Outcomes

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Abstract

Background Traumatic intracranial hemorrhage (TICH) and its progression have historically resulted in poor prognosis and functional disability. Such outcomes can impact the daily lives and financial condition of patients' families as well as add burden to the health care system. This review examines the diverse therapeutic intervention that were observed in randomized clinical trials (RCT) on various outcomes. Many demographic and clinical risk factors have been identified for poor prognosis after a TICH. Among the many therapeutic strategies studied, few found to have some beneficial effect in minimizing the progression of hemorrhage and reducing the overall mortality.

Methods A literature review was conducted of all relevant sources using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to include articles that were RCTs for patients aged 18 years and above to include a total of 19 articles.

Results Across studies, many therapies have been assessed; however, only few findings including infusion of tranexamic acid (TXA), use of β-blocker, and early operative evacuation of TICH yielded favorable results. Use of steroid and blood transfusion to target higher hemoglobin levels showed evidence of adversely impacting the outcome.

Conclusion Of the many therapeutic strategies available for TICH, very few therapies have proven to be beneficial

Keywords
- traumatic intracranial hemorrhage
- expansion
- interventions
- outcomes

Introduction

Traumatic brain injury (TBI) is defined as an interruption of brain function due to sudden damage to the head by a blunt or penetrating force.[1] Common causes of blunt trauma include injuries due to motor vehicle crashes, falls, sports, and assaults. Penetrating trauma includes gunshot or stab wounds, or injury due to impaled objects. TBI can present as mild injury such as concussions to a severe injury such as massive intracranial hemorrhage. Traumatic intracranial hemorrhage (TICH) is generally diagnosed with computed tomography (CT) imaging. Glasgow Coma Scale (GCS) is the most commonly used neurologic assessment tool for TBI. The scale ranges from 3 to 15 where 13 to 15 is mild injury, 9 to 12 is moderate injury, and 8 or lower is severe injury.

Severe TBI is associated with death and major disability. According to the Centers for Disease Control and Prevention (CDC), in 2014, an average of 155 people died daily from TBI-

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related injuries.[2] An estimated 13.5 million adults and children live with disability due to TBI in the United States, with the highest rate of TBI observed in older adults (older than 75 years) at a rate of 2,232 per 100,000.[3] Incurred medical costs and costs due to loss of productivity are estimated to be $76.5 billion annually, making TBI one of the largest expenditures in the health care system.[4]

TICH is a common and serious consequence of TBI. TICH can also be classified into brain contusion, epidural hematoma, subdural hematoma, intraparenchymal hemorrhage, and subarachnoid hemorrhage. TICH can continue to expand during the first several hours after initial injury resulting in further deterioration of the patient's condition.[5] Severity of TICH is identified by volume of the hemorrhage and impact on faculties. Repeat CT scans can show whether the hemorrhage has progressed or not. Prior study showed that more than 50% of hematomas expanded in the repeat CT scans following TBI.[6] Hemorrhagic expansion in the subsequent hours of injury can result in deterioration of the condition of the patient resulting in increase in operative intervention.[7] Over the past many years, a few factors have been identified for hemorrhagic expansion. These include older age, male gender, larger size of hematoma on initial CT scan, and coagulopathy.[7] Many interventions including therapeutic strategies have been tested to prevent the progression of hematoma. This review evaluates those approaches and outcomes by examining all randomized trials that have been conducted over the past 30 years.

Methodology

Databases PubMed, EBSCOhost, and OVID MEDLINE were searched for relevant studies by a single reviewer. The search was conducted to include publications from January 1990 to February 2021 using the following keywords:

"traumatic intracranial hemorrhage progression" or "traumatic brain injury, traumatic brain injury progression" or "brain injury bleeding progression" or "head injury bleeding progression" or "non-progressive traumatic intracranial hemorrhage" or "traumatic stable intracranial hemorrhage" or "traumatic constant intracranial hemorrhage."

Only patients ≥18 years were included. Only randomized controlled trials (RCT) were included in the current review. Meta-analyses, systematic reviews, retrospective review, and all other study types were excluded from the search. Studies were removed if they were not having or relating to TICH. Studies were also excluded if there was no mention of progression or the lack of. This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Additional articles were found using Google.

Results

A total of 19 randomized trials were identified and selected for the review (►**Fig. 1**).

Most studies used CT scans to diagnose TICH; only a few used magnetic resonance imaging (MRI). Initial imaging was performed on the patient at hospital presentation or within a few hours. The timing of repeat imaging varied between studies (►**Table 1**).

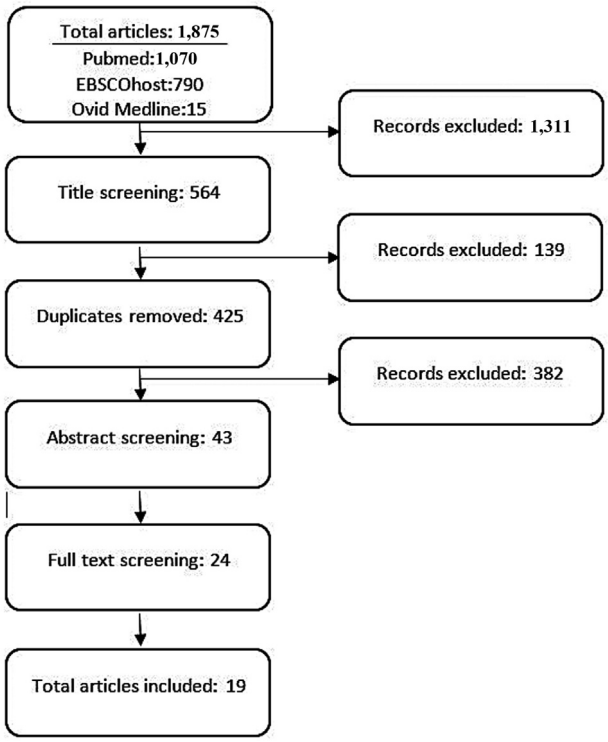

Fig. 1 PRISMA diagram for literature screening using the keywords "traumatic intracranial hemorrhage progression" or "traumatic brain injury, traumatic brain injury progression" or "brain injury bleeding progression" or "head injury bleeding progression" or "non-progressive traumatic intracranial hemorrhage" or "traumatic stable intracranial hemorrhage" or "traumatic constant intracranial hemorrhage."

Therapeutic Interventions

Coagulation Management

Tranexamic acid Infusion

Jokar et al performed a study, comparing tranexamic acid (TXA) versus placebo groups. Each group had 40 patients and the baseline characteristics of the two groups were the same including the initial TICH volume. The patients with GCS score ≤8 and volume of TICH ≥30 mL were excluded. The TICH group consisted of patients with epidural, subdural, and intracerebral hematomas. The follow-up CT scan after 48 hours of TXA administration showed significantly less progression of TICH in the TXA group.[8] A recent study, CRASH-3 (Corticosteroid randomisation after significant head injury) trial, enrolled 12,737 patients from 29 countries who presented with a GCS score of ≤12. Injuries were categorized from mild to severe but were not classified by TICH type. The primary outcome of the study was mortality. Instead of measuring the TICH volume expansion, the trial looked at the mortality within 24 hours of hospital admission and 28 days' mortality. Two doses of TXA were administered within 3 hours of injury and it was found that head injury–related deaths (within 24 hours) and 28 days' mortality were

Table 1 A description of studies collected for the review

Study	Country	Year	Study population	Type of TBI	Diagnostic tests	CT scan timing	Primary outcome	Study Conclusion
Jokar et al[8]	Iran	2017	Tranexamic acid group: 40 patients Placebo group: 40 patients	ICH	CT scan	48 h after TXA administration	Reduced ICH growth in TXA group versus placebo	Slowed progression of TICH in the group that received TXA
Roberts and Shakur-Still[9]	United Kingdom	2019	Tranexamic group: 6,406 patients Placebo group: 6,331 patients	ICH	CT scan	Admission CT scan	TXA reduces head injury mortality if given within 3 h of injury	Mortality within 24 h and within 28 d was significantly reduced in the TXA group
Fakharian et al[10]	Iran	2017	Tranexamic acid group: 74 patients Placebo group: 75 patients	TICH-SDH, EDH, SAH, Contusion, IVH	CT	CT at admission, follow-up CT 24–48 h after treatment	Short dose of TXA does not contribute to prevention of hemorrhage growth	No statistically significant differences were shown when stratified by bleeding type of analyzed by overall treatment groups
Ebrahimi et al[11]	Iran	2019	Tranexamic acid group: 40 patients Placebo group: 40 patients	SDH, EDH	CT	CT at admission, after surgery, and at discharge/ 7 d after surgery	TXA may reduce bleeding but results are inconclusive due to small sample size	TXA decreased the amount of bleeding during surgery but not after
Joseph et al[12]	United States	2013	18 of 22 patients remain non-functional, 4 of 6 maintained functional status after platelet transfusion	ICH	CT scan and platelet function test	Admission CT scan and repeat CT scan 6 h after platelet transfusion	Platelet transfusion does not improve platelet function and progress of ICH independent of platelet function	There was no improvement in patients regardless of bleeding type when administered with one pack of platelets to those taking 325 mg of aspirin
Zhang et al[13]	China	2019	LEFT group: 28 patients No LEFT group: 35 patients	SDH	CT scan and blood test	Before and after randomization	Low-dose early FFP transfusion associated with higher incidence of DTICH than the No LEFT group	LEFT therapy was associated with a higher incidence of newly developed delayed intracranial hematoma
Etemadrezaie et al[14]	Iran	2007	Fresh frozen plasma group: 44 patients Normal saline group: 46 patients	DTICH	CT scan	At the time of injury, repeated after 1 mo	Early FFP infusion may cause increase in DTICH and mortality	Early infusion of FFP resulted in higher rate of mortality
Narayan et al[15]	United States	2008	Recombinant factor VIIA group: 61 patients Placebo group: 36 patients	ICH	CT scan	Within 6 h of injury and repeated at 24 and 72 h	Less hematoma progression in intervention group vs. placebo group	There were no differences in progression of mortality, but a higher incidence of thromboembolic complication in the rFVIIa group
Allard et al[16]	Canada	2009	Coagulopathic patient group: 25 of 72 Noncoagulopathic group: 47 of 72	ICH	CT scan and blood test	At the time of injury and repeated in 48 h	ICH progression in 80% of coagulopathic patients vs. 36% without coagulopathy	Mortality rates were five times higher in coagulopathy patients as compared with their counterparts
Phelan et al[17]	United States	2012	Enoxaparin group: 34 patients Placebo group: 28 patients	Intracerebral hemorrhage	CT scan	CT scan at 24 h after injury and repeated after 48 h	Progression of TICH using enoxaparin	TBI progression in enoxaparin group is the same vs. placebo group
Grenander et al[18]	Sweden	2001	Antithrombin group: 13 patients Control group: 15 patients	Contusion, SAH, SDH	CT scan and blood test	Admission CT scan, at 2 d, and at 1 wk	Marginal reduction of hypercoagulation after antithrombin concentrate administration	No significant differences in reduction of hypercoagulation, progress of brain injury, ICU LOS
Mendelow et al[19]	United Kingdom	2015	Early surgery group: 82 patients Initial conservative t/t group: 86 patients	Intracerebral hemorrhage	CT scan	Baseline at the time of admission and follow-up at 5 d	Patients with GCS 13–15 can be managed conservatively; those with GCS 9–12 achieve the best outcome with early surgery	Early surgical evacuation created a survival advantage in patients with intraparenchymal hemorrhage and GCS of 9–12 but less effective in patients with GCS <9

(*Continued*)

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Table 1 (*Continued*)

Study	Country	Year	Study population	Type of TBI	Diagnostic tests	CT scan timing	Primary outcome	Study Conclusion
Prud'homme et al[20]	Canada	2016	Dexamethasone group: 10 patients Placebo group: 10 patients	chronic SDH	CT scan and MRI scan	Baseline at the time of injury and follow-up at 2 wk and 1, 2, and 6 mo	No clear beneficial effect of interventional group for t/t of chronic subdural hematoma vs. placebo	No significant differences in hematoma thickness but fewer surgical interventions. The therapy group experienced many side effects
Wang et al[21]	China	2017	20% mannitol group: 43 patients 3% hypertonic saline group: 40 patients	Moderate TBI	CT scan and blood test	Admission CT scan	No risk of intracranial rebleeding with hypertonic solutions	Hyperosmotic solution did not significantly affect coagulation function
Resnick et al[22]	United States	1994	Hypothermia group: 20 patients Normothermic group: 16 patients	DTICH	CT scan and blood test	CT scan 6 h after injury and repeated 12–24 h after injury	Hypothermia does not increase the risk of intracranial hemorrhagic complications and coagulopathy	Hypothermia has no significant effects in the incidence of delayed intracerebral hemorrhage or coagulopathy
Khalili et al[23]	Iran	2020	Beta blocker group: 102 patients Control group: 120 patients	TBI	CT scan	Admission CT scan or within 24 h of admission	Beta blocker group decreases in-hospital mortality and improves functional outcome	Treatment decreased in-hospital mortality and long-term functionality in severe TBI patients
Jiang et al[24]	China	2018	Atorvastatin group: 98 patients Placebo group: 98 patients	Chronic SDH	CT scan	Baseline admission and repeated after 8 wk treatment with atorvastatin	Hematoma volume reduction after 8 wk in the atorvastatin versus the placebo group	Atorvastatin significantly reduced the size of the hematoma for up to the 16-week follow-up and fewer patients required surgical intervention
Bai and Gao[25]	China	2018	Recombinant human erythropoietin(RHE) group: 60 patients Control group: 60 patients	Severe TBI	CT scan or MRI scan	Admission CT scan	No improvement of neurologic outcome in the interventional group vs. the control group	No significant differences in outcomes
Eisenberg et al[26]	United States	2019	I/V glyburide group: 15 patients Placebo group: 14 patients	Brain contusion	MRI scan	Baseline MRI before infusion of drug and repeated after completion of infusion (interval between two scans are 72 h)	IV glyburide may be safe in TBI. IV glyburide decreases hemorrhage + edema (lesion volume) and blood volume vs. placebo	No significant improvement in brain edema
Khalili et al[27]	Iran	2017	Oral glibenclamide group: 29 patients Placebo group: 23 patients	Brain contusion	CT scan	Baseline 0 d, days 3 and 7	Intervention group associated with decreased contusion expansion rate versus placebo	Treatment contained bleed but didn't improve functional disability assessment scores
Vedantam et al[28]	United States	2016	Total: 200 patients, randomly divided into transfusion group 10 mg/dL vs. 7 mg/dL	Brain contusion	CT scan and hemoglobin level	Admission CT scan and follow-up CT scan within 24 h with average time 15.2 hours between CT scans	Higher transfusion threshold of 10 mg/dL increase risk of progressive hemorrhagic injury events	Higher hemoglobin thresholds increased the risk of progressive hemorrhagic injury, incidence of delayed hemorrhage, longer ICU LOS, unfavorable outcomes

Abbreviations: CT, computed tomography; DTICH, delayed traumatic intracerebral hemorrhage; EDH, extradural hematoma; FFP, fresh frozen plasma; ICH, intracranial hemorrhage; ICU, intensive care unit; IV, intravenous; IVH, intraventricular hemorrhage; LEFT, low-dose early fresh frozen plasma therapy; LOS, length of stay; rFVIIa, recombinant factor VIIa; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; t/t, treatment; TBI, traumatic brain injury; TICH, traumatic intracranial hemorrhage; TXA, tranexamic acid.

significantly reduced in the TXA group when compared with the placebo group.[9]

A third study included 149 TBI patients in a randomized, double-blind clinical trial who received either TXA or a placebo of 0.9% normal saline. TBI included subdural hemorrhage, subarachnoid hemorrhage, contusion, intraventricular hemorrhage, and epidural hematoma. The primary outcome of interest was the growth of the hemorrhagic lesion, and the secondary outcomes were mortality, requiring brain surgery, Glasgow Outcome Scale (GOS) score, new source of bleeding, and mass effects. Hemorrhagic expansion did not show a statistically significant difference when stratified by bleeding type or when analyzed by overall bleeding type when comparing the placebo group to the TXA treatment group.[10] Finally, in a double-blind controlled clinical trial study, 80 patients, 40 who presented with subdural hemorrhages and 40 who presented with epidural hemorrhages, were evenly allocated into TXA and 0.9% normal saline treatment groups (placebo). The outcome of interest was the amount of bleeding both during and after surgery as well as the rate of the drop in hemoglobin. Results showed that for bleeding there was a statistically significant difference between the TXA and placebo groups during surgery but not after surgery. There was no statistically significant difference in the rate of hemoglobin decrease between the two groups before, immediately after, or 6 hours after the surgery had been completed.[11]

Platelet and Fresh Frozen Plasma Transfusion

The study by Joseph et al explored the outcome of platelet transfusion therapy by transfusing platelets to patients taking 325 mg aspirin. Patients presented with epidural, intraparenchymal, intraventricular, subarachnoid, or subdural hemorrhages. Administration of one pack of platelets did not improve platelet function and did not influence intracerebral hematoma progression overall.[12] The role of low-dose early fresh frozen plasma (FFP) transfusion treatment in preventing perioperative coagulopathy and improving long-term outcome in patients with severe TBI (hematomas) was also assessed. Two groups were compared: low-dose early FFP therapy (LEFT; 5 mL/kg) group that was given FFP on admission in the operating room and another group (No LEFT group) was given normal saline 5 mL/kg. The LEFT therapy group was associated with higher incidence of newly developed delayed traumatic intracranial hematoma as compared with the No LEFT group.[13] Similarly, Etemadrezaie et al examined the mortality in patients given either FFP or saline. TBI types included nonevacuated mass lesions, intracerebral hematomas, extra-axial hematomas, intraventricular hemorrhage, or subarachnoid hemorrhages. Patients with severe TBI who were given FFP did not show a significant difference in the worsening of the head injury when compared with the normal saline group. However, early infusion of FFP resulted in a higher rate of mortality. Results were not reported as stratified by injury type.[14]

Recombinant Factor VIIa

Narayan and colleagues investigated recombinant factor VIIa (rFVIIa) administration in TICH patients. The study was performed in 38 institutions from three continents. A total of 97 patients were enrolled in the study. The inclusion of the study required the presence of a minimum of 2-mL volume of hemorrhage on the baseline CT scan. The study found no significant difference in progression of TICH in the treatment group compared with the placebo group. There was no significant difference in 15 days' mortality between the rFVIIa (18%) and the placebo group (17%). A higher incidence of thromboembolic complication was found in the rFVIIa group.[15]

Coagulopathy Profile

Allard and colleagues looked at the relationship of severe TICH patients who presented with coagulopathy and hematoma expansion and mortality. Coagulopathy was defined as international normalized ratio (INR) $\geq$1.3, partial thromboplastin time (PTT) $\geq$35 seconds, or reduced platelet count $\leq 100 \times 10^9$/L. The study showed that coagulopathy was associated with intracerebral hematoma progression. Mortality was fivefold higher among coagulopathy patients as compared with those patients with a normal coagulation profile.[16]

Prophylactic Anticoagulation

Phelan et al performed a trial and enrolled 62 patients in the study. Thirty-four patients were randomized into an enoxaparin group and 28 were randomized to a placebo group. All patients had a small and stable TICH. The drug or placebo was given from 24 to 96 hours after injury and CT imaging was repeated 24 and 48 hours after injury. The enoxaparin in minor and stable TBI patients yielded the same effect as the placebo in terms of the progression of the TICH.[17]

Antithrombin Concentrate

The early administration of antithrombin concentrate was given to TBI patients to determine if it inhibits or shortens the time of hypercoagulability. All patients presented with brain contusions and 26 of 28 presented with an intracranial hemorrhage. Hypercoagulability was assessed by soluble fibrin (SF), D-dimer, thrombin–antithrombin complex (TAT), and routine coagulation tests. It was concluded that antithrombin concentrate administration to patients with severe TBI resulted in minimal reduction of hypercoagulation.[18] Other outcomes such as progress of brain injury and time spent in intensive care unit (ICU) were also not significantly different and the comparison of treatment and intracranial hemorrhage was not reported.

Operative Interventions

The Surgery (Trauma) for Traumatic Intracranial Hemorrhage (STITCH) trial examined the early operative intervention and evacuation of intraparenchymal hemorrhage volume of 10 mL calculated by: (length $\times$ width $\times\cdot$height)/2 in centimeters. Exclusion criteria included but was not limited to having an SDH or extradural hematoma that required surgery. Eighty-three of 170 patients were randomized into early operative intervention and 87 patients were managed conservatively. In patients with intraparenchymal hemorrhage, early surgical treatment of evacuation was found to have survival advantage in patients with GCS of 9 to 12. In patients with a GCS $<$9, surgical intervention appears to be less effective.[19]

Steroid Administration

The impact of dexamethasone on progression of the thickness of the hematoma and surgical intervention on patients with chronic subdural hematoma (SDH) was assessed. A total of 12-mg dexamethasone in three divided doses were given to the patients for 3 weeks followed by 1-week tapered dose. No significant differences were observed in terms of hematoma thickness and clinical changes in dexamethasone as compared with the placebo group, but a smaller number of patients had undergone surgery in the dexamethasone group as compared with the placebo group. However, patients experienced more side effects in the dexamethasone group as compared with the placebo group.[20] This was a pilot study with only 20 patients included in the study. Therefore, no definite conclusion can be drawn from the study.

Hyperosmolar Therapy

The effect of hyperosmolar therapy using either hypertonic saline or mannitol on coagulation was assessed in patients with moderate brain injury with GCS score of 8 to 12 with evidence of brain edema. Rotational thromboelastometry (ROTEM) parameters such as clotting time, clot formation time, maximum clot firmness, and standard coagulation tests such as INR, prothrombin time (PT), PTT, fibrinogen, and platelet count were measured. According to this study, the use of 3% hypertonic saline and 20% mannitol for the control of intracranial pressure did not significantly affect a patient's coagulation function. Researchers concluded that the hyperosmotic solution does not increase the risk of intracranial rebleeding.[21]

Hypothermia

Resnick et al examined the effect of hypothermia on the occurrence of delayed traumatic intracerebral hemorrhage and coagulopathy in patients with TBI. Patients with head injury were randomized into a normothermia group and a hypothermia group. Both CT imaging and blood tests were done to collect PT, PTT, and platelet count. Tests were done after injury and repeated after 24 hours. It was found that there was no significant difference in the incidence of delayed traumatic intracerebral hemorrhage and coagulopathy in both groups.[22]

Other Therapeutic Regimens

β-Blocker

The effect of β-blocker treatment on patient outcome such as in-hospital mortality and Glasgow Outcome Scale-Extended (GOS-E) score on discharge and at 6 months' follow-up was examined. In this study, patients with severe TBI were given either 20-mg propranolol orally every 12 hours for 10 days or no propranolol. The treatment group consisted of patients with epidural, subdural, subarachnoid or intraventricular hemorrhage, contusion, skull fracture, pneumocephalus, or craniectomies. Results stratified by brain injury type were insignificant however, the study found that propranolol decreases in-hospital mortality and improves long-term functional outcome in isolated severe TBI patients.[23]

Atorvastatin

Another study analyzed atorvastatin intervention in chronic SDH. The drug was given for 8 weeks. There was a significant reduction in size of the hematoma at 8 weeks and a fewer number of patients underwent surgical intervention in the atorvastatin group compared with the placebo group. This implied that surgical intervention might not be necessary for chronic SDHs when taking size and other factors into consideration. The positive neurologic effects remained during the follow-up of 16 weeks during the study period.[24]

Recombinant human erythropoietin

Bai et al evaluated the effects of recombinant human erythropoietin (RHE) for treating patients diagnosed with severe TBI defined as GCS $\leq$8. The patients were either administered 6,000 IU (international unit) of RHE or placebo (0.9% saline) by subcutaneous injection within 2 hours of admission and on the 3rd, 5th, 10th, and 15th day of admission. The primary outcomes measured included GOS score, mortality, and any adverse events. The therapeutic intervention did not show any significant difference in any outcome measures.[25]

Glyburide

Eisenberg et al conducted a pilot study to evaluate the safety and efficacy of intravenous (IV) glyburide and its effect on cerebral edema and hemorrhage compared with placebo in patients with TBI. A baseline MRI scan was done prior to the drug or placebo infusion and MRI was repeated after completion of infusion. It was found that the treatment with IV glyburide in patients with moderate to severe TBI may be safe, provided the blood glucose is monitored closely. glyburide infusion in this pilot study did not show any significant improvement in brain edema.[26]

Glibenclamide

The use of 5 mg of oral glibenclamide daily for 10 days was evaluated on the expansion of TICH, GOS, modified Rankin scale, and Disability Rating Scale. The study enrolled only 64 patients with brain contusion of $<$30 mL on the baseline scan. The study excluded patients who were diabetic and were on oral hypoglycemic agents. The study found significant containment of TICH in the treatment group compared with the placebo group. No significant differences were found in the treatment groups comparing functional disability of patients.[27]

Hemoglobin

Another study examined the hemoglobin threshold at 10 versus 7 g/dL on the progression of TICH among other outcomes. The higher threshold was kept by giving the blood transfusion. The study found higher hemoglobin threshold (10 g/dL) after severe TBI increased the risk of progressive hemorrhagic injury and had a higher incidence of delayed hemorrhage. Higher thresholds also resulted in prolonged length of stay in the ICU as well as unfavorable outcomes, as defined by GOS scores.[28]

Discussion

This article examined the existing RCTs conducted in the field of TBI specifically in TICH and found few therapeutic interventions favorable (►**Table 1**).

Many coagulation strategies have been tested in TBI to contain the expansion of TICH and only few have provided

favorable outcomes. In the CRASH-2 trial,[29] TXA administration within 3 hours of injury in trauma victims resulted in better survival compared with the placebo group. That became the motivation for the CRASH-3 trial.[9] The CRASH-3 trial displayed the positive effects of TXA in TBI patients when administered within 3 hours of injury. The results showed a reduction in mortality when given to mild to moderate head injury patients within this time period, supporting the outcome from the researchers' previous trial and the hypothesis.[9] However, the absolute difference in overall mortality in CRASH-2 and CRASH-3 trials were less than 2%. The results were statistically significant due to large sample sizes in the both trials. The use of TXA in hypotensive trauma patients or in TBI varies from institution to institution. One of the critiques among nonusers is whether the significant difference in mortality equates clinical significance. Other studies looked at the dosage and timing of TXA administration and concluded that the administration of TXA within a certain time frame could reduce ICH growth; however, larger studies are needed to compare appropriate dosage and administration timing.[8,11] Contrary to these findings in regard to TXA infusion, a recent study did not observe any clinical improvements.[10]

Coagulopathy is associated with increased progression of ICH and higher mortality in severe TBI patients.[16] This study showed a direct relationship of severe TBI with coagulopathy. Patients who presented with severe TBI with GCS score $\leq$6 were found to have significantly increased incidence of coagulopathy when compared with patients whose GCS scores were 7 to 8.[30] Coagulopathy was defined as abnormality on PT and PTT obtained on admission. Intuitively increasing the coagulation factors in the blood can result in reducing the expansion of hemorrhage. However, when the FFP was given to severe TBI patients during the operation, it showed higher incidence of delayed bleeding compared with patients who did not receive FFP.[13] Similarly, when the FFP was given to nonoperative TICH patients, it showed higher mortality rate in the FFP transfused group.[14]

rFVIIa was also trialed in TICH patients and was found to have no significant difference in expansion of hemorrhage or in short-term mortality.[15] There was a higher incidence of thromboembolic events in the rFVIIa group compared with the placebo group. When platelet transfusions were given to patients who had a history of aspirin regimen prior to injury, the outcomes were similar to that of the cohort of patients who did not receive the transfusion.[12]

When enoxaparin was administered as a prophylaxis for venous thromboembolism (VTE) on patients with identified TBIs, the TBI progression rate was low and the VTE rate was nominal.[17] Grenander et al investigated the effects of antithrombin, an anticoagulant, to counterbalance the potential damage of hypercoagulation after trauma. The study did not result in any significant findings.[18]

Timely operative intervention in space-occupying intracranial hemorrhage is one of the factors associated with survival in severe TBI patients. Mendelow et al studied the effects of early surgical evacuation of hematoma by performing a craniotomy as compared with more conservative treatment. Due to the early termination of the study from lack of enrollment, researchers were unable to gather reliable evidence to support their findings. However, preliminary analysis showed that early evacuation may be more beneficial depending on the GCS score.[19]

Prud'homme et al considered the effects of the corticosteroid dexamethasone on chronic SDH patients. Corticosteroids have been known to reduce inflammation, and promote neovascularization, and fibrinolysis. However, due to a small sample size, it cannot strongly support the hypothesis that dexamethasone would be beneficial to chronic SDH.[20]

Jiang et al studied the use to atorvastatin in the use of chronic SDH patients. Atorvastatin was expected to reduce inflammation in the vessel wall and prevent hematomas. This study supported the hypothesis that atorvastatin may be a safe alternative for a conservative or nonsurgical approach.[24]

Hyperosmolar therapy was used by Wang et al to assess the use of a hypertonic solution opposed to mannitol. Researchers hypothesized that sudden hydration would cause coagulopathy; therefore, a hypertonic solution may be beneficial in managing TBI. The use of hypertonic 3% NaCl or 20% mannitol did not increase the risk of a rebleed and both are considered safe.[21]

The impact of hypothermia has been disputed for decades. Resnick et al studied the effects of using hypothermia on patients to prevent delayed traumatic intracranial hemorrhage (DTICH), cooling the patients to temperatures of 32 to 33°C. Cooling the patients was intended to decrease thromboxane A2, a vasoconstrictor that prevents platelet adhesion. Use of hypothermia did not result in significant differences in the occurrence of DTICH or coagulopathy between the groups.[22]

β-blockers are used in TBIs to counterbalance the adrenergic storm caused by a brain injury. This treatment is a novel concept and found to have favorable survival rates.[23]

RHE was examined by Bai and Gao under the pretense that this treatment can promote neurogenesis and angiogenesis. They did not find any significant difference in outcomes in severe TBIs.[25]

Two studies examined the hypoglycemic medications in TBI with variable results.[26,27] Eisenberg et al studied the effects of glyburide in TBI patients. This drug is expected to inhibit the SUR1 and TRPM4 variants, which are linked to cerebral swelling and edema. Though a small trial, the findings were insignificant, and the drug showed no clinical benefits.[26] Khalili et al assessed the use of glibenclamide on the SUR1 channel as well. Khalili et al's results showed a decrease in contusion expansion rate depending on severity of TBI but no recovery in functional disability.[27]

Vedantam et al hypothesized that to prevent secondary injury and anemia in TBI patients, administering packed red blood cells to maintain a hemoglobin threshold at a higher level after injury would be paramount. However, keeping the hemoglobin at 10 g/dL by blood transfusion adversely influenced the outcome.[28]

Patient's injury type, neurologic status, volume of hemorrhage, GCS score, and some demographic characteristics

including advanced age and prior history of certain conditions may all be factors that help the physician to decide on the best therapeutic option to employ.

Limitations

The review conducted explored various treatment options for TICH; however, the effect of therapeutics varies between the specific injury type presented. The quality of collected studies was also not evaluated. Some studies did not report the analysis of specific injury type by each discussed therapeutic; therefore, this review is limited to analyzing therapeutics across TICHs as a general focus. Further studies can analyze each therapy by TICH type given a large enough sample size.

Conclusion

Out of many therapeutic interventions, only few modalities including infusion of TXA, use of β-blocker, and early operative evacuation in TICH yielded favorable results.

Availability of Data and Material

Data used in this study were collected from prior studies and are available for use.

Ethics Approval

This study was exempt from requiring ethics approval because this was a review of existing studies and did not involve human or animal participants.

Authors' Contributions

A.S. and R.T. collected and analyzed the resources, and wrote the manuscript. N.A. is the Principal Investigator and corresponding author, and conceived and designed the review, collected and analyzed resources, and wrote the manuscript.

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None.

Conflict of Interest

None declared.

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