A Narrative Review on Translational Research in Acute Brain Injury

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Abstract

There has been a constant endeavor to reduce the mortality and morbidity associated with acute brain injury. The associated complex mechanisms involving biomechanics, markers, and neuroprotective drugs/measures have been extensively studied in preclinical studies with an ultimate aim to improve the patients' outcomes. Despite such efforts, only few have been successfully translated into clinical practice. In this review, we shall be discussing the major hurdles in the translation of preclinical results into clinical practice. The need is to choose an appropriate animal model, keeping in mind the species, age, and gender of the animal, choosing suitable outcome measures, ensuring quality of animal trials, and carrying out systematic review and meta-analysis of experimental studies before proceeding to human trials. The interdisciplinary collaboration between the preclinical and clinical scientists will help to design better, meaningful trials which might help a long way in successful translation. Although challenging at this stage, the advent of translational precision medicine will help the integration of mechanism-centric translational medicine and patient-centric precision medicine.

Keywords

- acute brain injury
- translational research
- subarachnoid hemorrhage
- traumatic
- brain injury
- acute ischemic stroke

Introduction

The word translational research (TR) means the transformation of laboratory discoveries into new therapeutics. The popularly used term "bench to bedside" signifies this concept where results of preclinical studies (bench) are directly used for the development of new diagnostic, preventive and treatment modalities for patients in clinics (bedside). The word "translational research" is almost synonymous to laboratory and animal studies which help to produce treatment options for the patients. However, it also extends to the enhancement of adoption of best practices at the community level so that it ultimately improves the health outcomes of the patients or the population. TR is defined by the European Society for Translational Medicine as an interdisciplinary branch of the biomedical field that is supported by three main pillars: bench side, bedside, and community.[1] The definition of TR has undergone continuous refinement from a two-stage model to three-stage and a recent five-stage model that signifies bench-to-bedside and back-to-bench research.[2] The T1 phase includes the early-phase clinical development that encompasses the application of results of laboratory tests for early human testing. This includes phase I and phase II clinical trials. In the T2 phase, the findings are further clinically tested (phase III trials) and integrated into clinical practice guidelines. T3 deals with the dissemination of knowledge obtained from prior steps to the community level and health services research. T4

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concentrates on using scientific knowledge for disease prevention by raising awareness about lifestyle and behavioral modification so as to have a positive population health impact. The T5 stage deals with involving certain other areas like social health, access to education, and health care that are essential to have a positive impact of interventions. In the T0 phase, patient and community-based findings are used to generate a new hypothesis that again goes for basic research, forming a continuum (►**Fig. 1**).

Acute Brain Injury

(ABI) remains a constant challenge in terms of the mortality and morbidity it produces. The complex mechanisms involved in ABI, biomechanics, markers, and neuroprotective drugs/measures have been extensively studied in preclinical studies with an ultimate aim to improve patients' outcomes. Despite a huge amount of research, only few have in principle been successfully translated into clinical practice. In this review, we shall be discussing important TR aspects related to traumatic brain injury (TBI), aneurysmal subarachnoid hemorrhage (aSAH), and acute ischemic stroke (AIS). For this narrative review, a PubMed literature search of the following terms used between 2010 and January 2020 was performed – "translational research," "bench to bedside," "aneurysmal subarachnoid hemorrhage," "traumatic brain injury," and "acute ischemic stroke."

The search was limited to English language reviews and original research articles of patients, and the titles and abstracts were read to obtain relevant studies. Pertinent historical papers and case reports were also included.

TR in TBI

TBI affects millions of people worldwide annually, resulting in significant loss of productive years and increased health care expenditures. The morbidity inflicted involves years of physical impairment, limited job performance, cognitive, and neuro-behavioral disturbances. In spite of enormous research, the treatment options are limited and more or less involve optimization of physiological parameters. The positive results observed in preclinical studies often fail to improve outcomes when put into clinical human practice. This is mainly due to heterogeneous TBI population in clinical trials, inappropriate TBI severity classification depending only on Glasgow Coma Score (GCS), variable outcome parameters in different trials, and the choice of experimental model.[3] The heterogeneity of TBI lies in the fact that the extent of contusions, edema, ischemia, raised intracranial pressure (ICP), hemorrhage, and secondary injury varies from person to person and is difficult to quantify just by the use of GCS.

The pathophysiological changes of TBI vary from person to person even if the GCS value is the same. The experimental model of animal studies involves the production of either focal, diffuse, mixed, complex, penetrating, or blast-induced injury which might not be entirely similar to what happens in the actual clinical state. To overcome this, TBI-relevant models have been suggested that focus on pathological changes produced such as SAH, hematomas, or ischemia rather than mechanics of brain trauma.[4] Rodents that are used as experimental models have a bony structure of skull with lissencephalic brain and little white matter which is different from the human skull structure having gyrencephalic brain with more white matter.[5] As a result, the findings from those

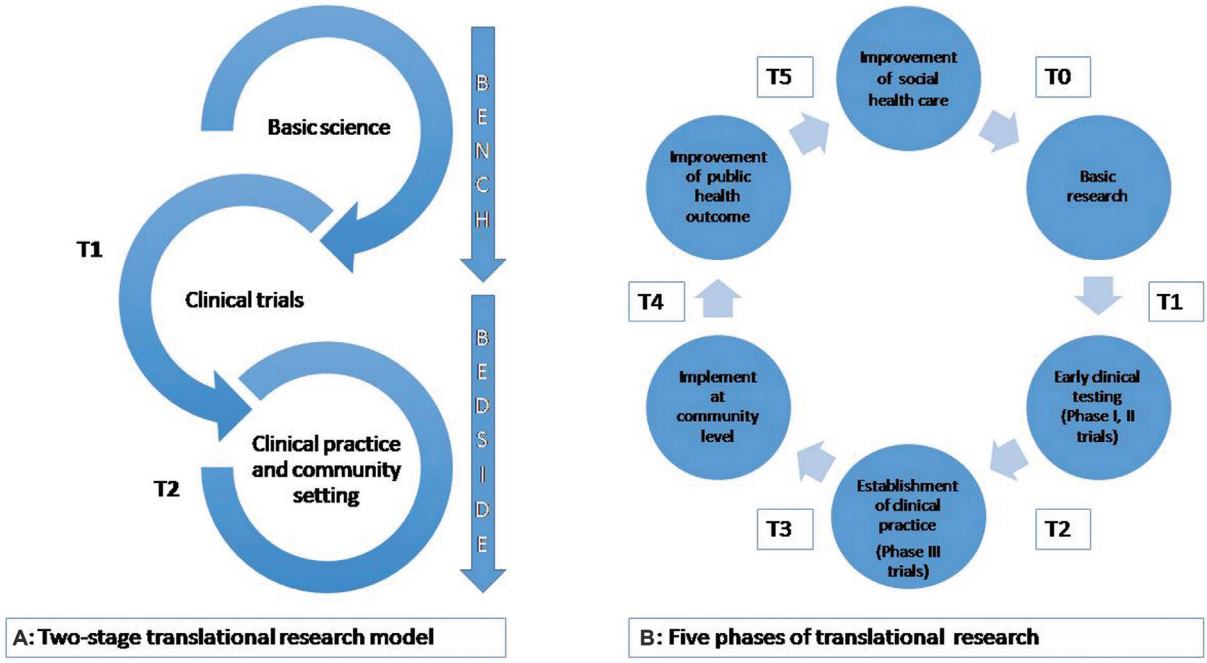

Fig. 1 The translational research models have been transformed from (**A**) two-stage model (T1–T2) to (**B**) five-stage (T0–T5) translational research model depicting a continuum from bench-to-bedside and bedside-back-to-bench research.

experimental trials cannot be directly translated for human TBI patients. Pig/sheep and non-human primate models more closely resemble human brain structure, and these large animal models are better experimental models.[6] The initial mechanical impact produces parenchymal and vascular injury; a secondary cascade of molecular injury sets in producing edema, inflammation, excitotoxicity, impaired autoregulation (AR), glial cell dysfunction, and neural degeneration. This secondary injury is the only available therapeutic target which can alter the outcomes of these patients. One of the main determining factors is the cerebral compliance and degree of ICP in these patients. After the initial pressure-volume indices measured in feline models failed to gain popularity,[7] the indirect measures of cerebral compliance such as ICP waveform/amplitude analysis and noninvasive measures of cerebrovascular reactivity like pressure reactivity index (PRx), pulse amplitude index (PAx), and optimal cerebral perfusion pressure (CPPopt) are the focus of research. For the purpose of validation of ICP-derived indices of cerebrovascular reactivity against the lower limit of autoregulation (LLA), 12 white New Zealand rabbits were retrospectively studied using an intracranial hypertension model. ICP, TCD, laser Doppler flowmetry, and arterial blood pressure (ABP) were recorded. LLA and indirect indices of cerebrovascular reactivity like PRx and PAx were derived. Both PRx and PAx were found to be in agreement with LLA.[8] In another retrospective study, relationship between cerebrovascular reactivity (determined by ICP-derived indices) and LLA was explored in the arterial hypotension model.[9] The physiological data were collected from piglets that underwent controlled hypotension by inflating a balloon catheter in the inferior vena cava. Measurement of ICP, ABP, and CBF by cortical laser doppler flowmetry was performed. PRx, PAx and correlation coefficient between pulse amplitude of ICP and CPP (RAC) were calculated. All the three indices, PRx, PAx, and RAC successfully predicted the LLA with PRx being superior among these three. Although PRx is a promising tool as a therapeutic target, it has still not been incorporated in regular clinical use. These indices have been used to provide personalized treatment targets to improve the outcomes of TBI patients. It has been observed that time spent with CPP below LLA derived from "CPPopt" is associated with increased mortality despite aggressive CPP- and ICP-oriented therapies.[10] Kramer et al did not find a conclusive association between ΔCPP (deviation of actual CPP from CPPopt) and outcomes, but time spent below CPPopt was associated with poor outcomes especially in patients with impaired AR.[11] The cerebral effect of vasoactive drugs on the preclinical model of TBI has shown that the choice of drug affects AR and CPP.[12] The elevation of mean arterial pressure (MAP) to improve CPP after TBI is insufficient alone to improve outcomes, and maintenance of AR is also an important factor in determining the final outcome.[13] Although early data suggest that dopamine should be considered as a first-line treatment to protect AR and improve outcomes, still further basic research is required to see the associated capillary blood flow changes and neurotoxic changes.[12]

The choice between mannitol or hypertonic saline for reducing ICP still eludes us. Both these agents are considered to modulate polymorphonuclear neutrophil (PMN) and endothelial cell (EC) activation. To compare their PMN–EC interaction and anti-inflammatory effects, CD1 male mice having induced TBI were administered an equimolar dose of 20% mannitol or 5% hypertonic saline (HTS).[14] In vivo PMN–EC interactions in pial venules were observed using intravital video microscopy. The authors concluded that both have similar effects on PMN–EC interactions, but further studies are needed to determine more subtle effects on blood–brain barrier (BBB) and PMN–EC interaction. In another study, authors compared the peri-contusional recruitment of leukocytes after TBI.[15] Controlled cortical impact was induced to 30 CD1 mice who were then randomized to five groups each receiving either HTS, mannitol, normal saline, progesterone, or sham. Live pial microscopy was used to study leukocyte–endothelial interactions and immunohistochemistry for the quantification of brain PMN. Mannitol showed lowest in vivo leukocyte recruitment and the lowest accumulation of leukocytes in injured brain as compared with HTS and progesterone.[15] However, the same cannot be confidently said for the human TBI which is much more complicated and perplexing. Systematic reviews and meta-analysis have failed to prove clear superiority of one agent over another in lowering ICP.[16–18]

BBB dysfunction exacerbates the cerebral edema resulting in increase in ICP and worsening of secondary brain injury. AQP4 is a type of aquaporin isoform, located on end-foot processes of astrocytes which is involved in the regulation of cerebral edema. Its role is quite complex and may facilitate increase or decrease in edema depending upon tissue characteristics, time post-injury, osmotic gradient, and interaction between other channels. While it is believed to be beneficial in the resolution of vasogenic edema, it may also worsen cytotoxic edema. Several agents like bumetanide, acetazolamide, and methazolamide have been used as inhibitors but without much success. In clinical practice, we have been unable to reap any beneficial results because of the failure of recognition of a specific inhibitor of AQ4 channels. Small interfering RNA (SiRNA) injected lateral to trauma site in postnatal day 17 rats who have sustained simulated TBI showed improvement in motor function and in spatial memory at 60 days after injury. This needs to be further studied in preclinical trials.[19]

The neuroprotection in TBI still relies on the optimization of physiological parameters as none of the agents have been successfully translated into clinical practice. Ghrelin, a neuroendocrine hormone, has been found to diminish brain injury and promote functional recovery. The downregulation of fibroblast growth factor and fibroblast growth factor-binding protein, upregulation of UCP-2, increased expression of p-Akt and Bcl-2, decreased Bax expression are some of the molecular mechanisms responsible for its neuroprotective property.[20,21] The research related to proposed neuroprotective agents is still limited to the preclinical phase. The nerve growth factor is another hormone which helps in neuronal growth, differentiation, and restoring function of injured brain cells. Experimental studies have used it for intranasal administration to bypass BBB and have found it to

reduce cerebral edema, improve motor function, and potentially provide neuroprotective effects.[22,23] The results of a human phase 2 clinical trial will further define its effect on neurological outcomes in TBI.[24] In their first case report, Chiaretti et al have confirmed its efficacy in improving functional outcomes when administered intranasally to a child with severe TBI.[25] Progesterone, a steroid hormone, has shown positive in-vivo results of inhibiting neuronal apoptosis, attenuating cerebral edema, decreased free radical damage, and cytokine production. In the ProTECT II trial, 100 patients having moderate-severe head injury were randomized to receive either progesterone or placebo for a total of 3 days.[26] Functional outcomes were assessed at 30 days post-TBI, the patients with severe TBI had lower mortality but worse functional outcomes compared with controls. Patients with a moderate head injury who received progesterone had a better 30-day outcome. No serious adverse effects of progesterone were observed in this study.[26] After these initial encouraging results in phase II trials, phase III trials were undertaken, but these failed to show improvement in the outcome.[27,28] This failure highlights the inadequacy of our capability to translate experimental data to human TBI. This again puts into perspective the possible reasons of failure that we have discussed earlier. Precisely defining TBI, improving animal studies, choosing the correct quantitative measure of outcomes, selection of patients, correct design of trial, its execution, and data handling are few of the steps which should be adhered to, in trials.[29] TBI Endpoints Development research program has been initiated with an aim to design and develop better clinical trials for TBI interventions.[30] It also aims to create a meta-dataset from other large datasets such as Transforming Research and Clinical Knowledge in Traumatic Brain Injury, Concussion Research Consortium, TBI-care, and many other multi-institutional and multidisciplinary groups having established clinical research networks. This will help examine the records and also find methods to improve the future trial designs.

Similarly, experimental designs of hypothermia showed beneficial effects on preclinical TBI models. However, this also failed as a neuroprotective measure when put into clinical practice. Olah et al performed a meta-analysis by calculating the cooling index, which is an integrated measure of therapeutic hypothermia. The authors found no difference in outcomes between the two groups and interstudy heterogeneity was very high. When they analyzed those randomized controlled trials (RCTs) that were homogenous with regard to statistical and clinical designs, they found hypothermia to be beneficial if the cooling index was high. The authors concluded that high heterogeneity could be the reason that beneficial effects have not been found in earlier studies.[31] In addition to the several factors already discussed, the therapeutic time window for instituting hypothermia holds much importance and needs to be established in that restricted duration of time to be effective. Another critical factor associated with hypothermia is the rewarming phase which should be slow lest not to lose all the benefits of cooling. Trials concentrating on devising new methods for inducing hypothermia, identifying specific biomarkers to assess treatment effect, and using specific brain hypothermia may show the right path to follow.[32] Nevertheless, the need is to generate a new hypothesis from the available data and test it in basic and preclinical studies to develop a new therapeutic intervention that further goes back to the T0 phase of TR.

The production of reactive oxygen species during early brain injury (EBI) is implicated as an important factor in secondary brain injury. N-acetylcysteine (NAC), an antioxidant, has shown promising results as a neuroprotectant agent in animal studies but the lack of well-designed human RCTs limits its definitive interpretation.[33] Clark et al performed a randomized phase I clinical trial assessing the effects of NAC in combination with synergistic adjuvant probenecid on children with severe TBI. Although this combination has not been tested earlier in animal studies, the authors suggested that treatment with this combination is feasible and devoid of adverse side effects and needs to be further studied in phase II and III trials.[34]

Mesenchymal stem cell therapy has possible neuroprotective ability following TBI. It enhances neurotrophic and immunomodulatory abilities, promoting neurogenesis, angiogenesis, and vascular stability. Human cell therapy is associated with an improved behavioral outcome in preclinical studies. However, a meta-analysis of animal studies to evaluate the efficacy of human stem cell therapies showed that the methods were too heterogeneous to allow comparisons and significant bias compromised the quality of these studies.[35] This reiterates the importance of systematic review and meta-analysis of experimental studies before proceeding to human trials. An optimum approach for the delivery of stem cells in a clinical setting still eludes us. Encapsulated cell biodelivery for stem cell therapy in the central nervous system is under study and still requires extensive experimental research.[36]

The inability to find neuroprotective drug has been mainly due to an incomplete understanding of secondary brain injury, inadequate basic science research, unclear therapeutic time window, treatment duration, and variability in design of clinical trials.

TR in AIS

AIS is one of the leading cause of morbidity and mortality in an older population. It has remained a field of immense research, but tissue plasminogen activator and endovascular clot removal techniques are the only ones which have been successful in improving patient outcomes. The therapies which proved beneficial in animal models failed in clinical trials resulting in the wastage of economic as well as time resource. Stroke Therapy Academic Industry Roundtable (STAIR) has provided a set of recommendations for carrying out effective TR.[37] The choice of correct animal model is the first step keeping in mind the difference in neurovascular anatomy, collateral circulation, and reperfusion characteristics.[38] Although rodents are relatively economical and have a similar vascular structure, non-human primates with gyrencephalic brains may be a better choice but are limited by cost and ethics issues. The inclusion of age criteria and

comorbid conditions like hypertension, diabetes, or hypercholesterolemia along with their respective co-morbid medications in animal stroke models is essential for simulating human stroke and for effective translation.[37] The experimental ischemic stroke model should resemble human stroke as closely as possible, and for this, size of infarct produced, duration of ischemia, time window, and physiological monitoring like blood pressure, blood glucose, blood gases, and temperature should be considered as all these parameters affect the outcomes. Monitoring cerebral blood flow (CBF) by laser Doppler flowmetry or perfusion imaging is considered essential to ensure appropriate induction of experimental ischemia.[38] The time of administration of therapeutic agent holds importance in stroke models, and one that is effective beyond 3 hours after ischemia can be very important for the clinical purpose. The use of polypharmacology that is capable of affecting multiple pathogenetic steps, optimum amount, and clinically relevant route of drug administration are other important things on which success of effective translation depends.[38] As discussed earlier, the quality of the preclinical trial (sample size, randomization, allocation concealment, and blinding) is important before its results are tested further.[39] Poor quality animal studies generate unreliable data and failure of clinical studies. Multicentric preclinical trials and systematic reviews have also been suggested to be performed before testing in a clinical trial. Cochrane has also established a preclinical animal study methods group to encourage the preparation of systematic reviews of basic animal research.[40] The negative findings are as important as positive results and should be reported clearly. The assessment of outcome parameters in preclinical studies is usually different from that used in clinical studies that may have an important impact on the translation of research findings. STAIR recommends using the infarct area and two distinct sensorimotor function tests in animal studies. In 2016, the National Institute of Neurological Disorders and Stroke (NINDS) organized a workshop on TR and gave a few recommendations.[41] In addition to the abovementioned measures, they emphasized on interdisciplinary collaboration between the preclinical and clinical scientists to design better and appropriate trials. The creation of stroke repositories can be immensely beneficial for gathering and analyzing data effectively. NINDS have established StrokeNet to conduct phase I/II and III trials which can ensure the conduct of good quality trials. It can also facilitate reverse translation by providing data to preclinical researchers who can plan their studies based on the clinical significance. Similarly, the clinical trials also need to include a homogenous population in terms of type of stroke, its mechanism, location, size, severity, and presence of collaterals.[41]

Anesthesia has long been questioned for its neuroprotectant or neurotoxic effect. Depending upon the species, excitotoxicity, neural network, collaterals and molecular action dose; anesthetic drugs may have a varied effect on stroke models. Studies have been performed to find out whether the choice of anesthesia improves the outcome. Animal studies have found a neuroprotectant effect of anesthetics on focal cerebral ischemia, but this has not been translated into clinical trials. Archer et al performed a systematic review on anesthetic neuroprotection in experimental stroke in rodents.[42] They found a 22 to 30% reduction in neurological injury in the setting of focal ischemia. Anesthetic exposure 1 to 2 days prior to ischemia provided greater neuroprotection than exposure in the immediate preischemic period.[42] Majority of the studies included a small sample size pointing toward the need for preclinical studies with a larger sample size. Anesthetic neuroprotection failed in female animals, aged animals, and those having comorbid conditions.[42] This points that stroke models that include young male rodents may not rightly reflect human stroke.

Several agents have been studied till date, but all have been futile in improving patient outcomes. Intravenous tissue-type plasminogen activator (tPA) and mechanical thrombectomy are the only standard modalities of treatment available. Patients with minor stroke or TIA are administered clopidogrel plus aspirin for the reduction of stroke recurrence.[43] The genotype is now increasingly being recognized to influence the risk profile for stroke as well as response to treatment. CYP2C19 allele status is considered as a possible determinant of the clopidogrel efficacy but still the relation is not yet clearly established.[44,45] Neuroinflammation is considered an important pathophysiological mechanism of cerebral damage in AIS. Experimental studies related to inflammation-modulating agents have shown promising results but failed in clinical trials. Recombinant human interleukin 1 receptor antagonist, minocycline, and natalizumab are some of the agents which have failed to show a clear benefit in clinical trials.[46–48] Recently, the effect of natalizumab was tested in a double-blind phase 2b trial on functional outcome after AIS. The authors found no improvement in patient outcomes in the study group.[49] Similarly, hypothermia acts at various pathophysiological steps and has been tested as a neuroprotectant in several AIS trials. Despite several positive results in experimental focal cerebral ischemia models, it could not be established as a treatment modality in clinical trials. The various hitches were the time window for cooling, ideal way to induce hypothermia, optimum temperature to be maintained, rapidity and time of cooling, rewarming rate, and management of various associated complications. The Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L) trial confirmed the feasibility and safety of intravascular cooling but found a higher incidence of pneumonia in the group instituted to hypothermia and antishivering treatment.[50] The intravascular cooling in the treatment of acute stroke 2 trial (ICTuS-2) was undertaken to assess whether changes in the original protocol could reduce the risk of pneumonia in the hypothermia group. Although it was stopped early, the incidence of mortality and pneumonia was 15.9 and 19% in the hypothermia group versus 8.8 and 10.5% in the normothermia group.[51] Recently, a phase III clinical trial was stopped early because of the lack of feasibility of cooling.[52] Overall, in clinical trials, hypothermia has been associated with increased complications.[53] This further highlights the need for establishing an effective and safe hypothermia regimen for AIS patients. Sonothrombolysis

uses pulsed-wave ultrasound to accelerate clot lysis and allow penetration and more exposure to intravenous tPA. Despite encouraging results in animal studies, a multi-centric, phase-3 trial RCT did not find any clinical benefit at 90 days.[54]

Biomarkers can be especially important in the diagnosis, treatment, and prognostication of AIS patients. As it was difficult to rely on a single marker for providing the picture of the complex ischemic episode, a panel of biomarkers was considered to be more reliable. However, none has been validated for use in human clinical stroke. There is a huge scope for studying biomarkers as a part of reverse translation in animal studies. The biomarker found to be relevant in clinical studies can be further studied in detail in animal experimental stroke models for its validation and drug development. The markers for cognitive decline after stroke have also been studied intensively. It has been suggested that the combination of rheumatoid factor, matrix metalloproteinase-9, and total homocysteine can help in the risk prediction of cognitive impairment among ischemic stroke patients with elevated blood pressure.[55]

Remote preconditioning has been found to confer both early and late brain protection against sustained ischemic-reperfusion injury in preclinical studies. In the absence of a conclusive modality of implicating preconditioning, several clinical trials are undergoing to study its efficacy.[56,57]

Stem cell therapy is a novel approach for improving recovery after stroke. In animal models, delivery of stem cells has been seen to improve outcomes by multifactorial action. The optimal time window for its administration, dosage, route of administration, type of stem cells, and their availability are few of the challenges involved in therapy. The clinical trials yet have not been able to replicate the experimental results but the quest is still on for its effective translation.[58,59]

TR in aSAH

aSAH is a type of stroke seen in a relatively younger age population and is associated with significant mortality and morbidity. The early brain injury (EBI), rebleeding, vasospasm, and delayed cerebral ischemia (DCI) are the major pathophysiological mechanisms on which the final outcome depends. The experimental animal models more common in use are the ones that use the direct injection of blood into subarachnoid space or endovascular perforation of a cerebral artery. Although this allows the evaluation of the effect of subarachnoid blood thereon, it essentially lacks the simulation of the clinical picture where the cerebral aneurysm is also associated with endothelial changes and pro-inflammatory state.[60] An animal model involving spontaneous aneurysm formation and rupture would be ideal for experimental studies, and this requires the generation of genetically engineered animals which resemble human cohorts more closely. DCI is usually studied in rodents either by post-mortem histological analysis, by gel casting followed by imaging, by angiography, or by magnetic resonance imaging, with each having its own shortcomings. The timing of onset of vasospasm and its quantification vary in rodent models and usually the outcome is not so severe as observed in humans. Along with these, the measurement of trends of physiological parameters like MAP, CBF, ICP, and CPP is also essential during preclinical studies. As in other models of acute brain injury, the outcome parameters need to be clearly defined to help translate the findings. A recent systematic review and meta-analysis of methodological quality of animal studies of SAH revealed several shortcomings. The authors suggest the registration of preclinical experiments, strict editorial and reviewer policy, and increased efforts in the education and training of researchers in laboratory practice.[61]

Several agents like magnesium, endothelin antagonists, statins, and tirilazad have failed to improve outcomes in human clinical trials. The failure of therapeutics that targeted vasospasm in particular, leads to the concept of EBI too being an important determinant of secondary brain injury and outcome. The sudden rupture of aneurysm resulting in arterial bleeding leads to a sudden transient increase in ICP and a temporary intracranial circulatory arrest. This produces global ischemia, decrease CBF, loss of AR, BBB dysfunction, ionic dysregulation, cortical spreading depolarization, neuroinflammation, impaired microcirculation, apoptosis, and activation of other molecular pathways. The influence of ICP variability on acute changes after SAH was studied by modulating blood injection velocity and composition in an experimental model of SAH. Animals undergoing rapid injection of blood developed secondary and sustained disruption of cerebral AR possibly contributing to EBI.[62] The variability in volume and speed of injection of blood, removal of cerebrospinal fluid before injection, and maintenance of blood pressure have cast a doubt on the comparability of results of various studies. The upcoming research needs to focus on the attenuation of EBI for improving outcomes after SAH.[63] While agents like erythropoietin, fluoxetine, atorvastatin, melatonin, mesenchymal stem cells, and several more have shown benefits in decreasing EBI in animal models, their effective translation into clinical use remains to be seen.[64–66]

DCI is not always caused by larger artery vasospasm, and these entities are considered separate now. In a recent systematic review of animal models of SAH, authors found that DCI developed more commonly in primate models with almost a similar incidence to humans and should be used for recapitulating aSAH rather than dogs, rats, rabbits, and mice.[67] However, the ethical issues and cost factors limit such experimental models. The cortical spreading depolarization and micro-thrombosis might not affect animals to the same extent as humans, and the rate of clearance of blood also varies among species. Moreover, variability in the definition of DCI and its detection by regular longitudinal follow-up has been one of the major hurdles. Digital subtraction angiography and magnetic resonance angiography are better alternatives to detect vasospasm rather than terminal histological analysis of animal brain tissue where the chance to follow-up is lost. Early neuroimaging can provide a reference for CBF supply which can help detect any supply–demand mismatch in subsequent scans. But the timing of vasospasm

varies among animals too, and the cost and labor involved make it difficult to carry out these imaging techniques in a timely manner. These should be taken into account while planning an experimental study as well as deciphering the results of an animal study.

Studies pertaining to several biomarkers of different kinds, related to molecular level and cellular level, biomarkers of cell death and recovery, inflammation and vascular function, and genetic and extracellular biomarkers are present in the literature. Osteopontin is an inducible extracellular matrix protein that has been suggested as a useful prognostic biomarker in SAH.[68] Experimental studies have found that its administration is associated with post-SAH BBB stabilization.[69] However, none of these have been classified as core biomarker due to the lack of validation and need to standardize research methodology. The development of biomarker panels which reflect several pathogenetic pathways may help to comprehend this multifactorial condition.[70] Lately, noncoding ribonucleic acids (RNAs) like micro-RNAs, SiRNAs, and long non-coding RNAs are being studied as biomarkers to predict the development of intracranial aneurysms and SAH.

Nimodipine is the only approved drug for improving outcomes after aSAH, but dose-limiting hypotension remains a significant concern. Local delivery of nicardipine by implanting pellets intracranially was seen to improve outcomes in initial trials. Since then, several different routes like intrathecal, intraventricular via external ventricular drain (EVD) or into subarachnoid space intraoperatively, have been tried. A novel local nicardipine delivery system when placed intracranially reveals vasoactive action and lack of toxicity.[71] Similarly, EG-1962 is a nimodipine microparticle sustained release formulation that showed positive results in preclinical studies. A phase III trial was undertaken with an aim to determine the efficacy of EG-1962 placed intraventricularly compared with the standard of care oral nimodipine. An interim analysis showed no significant increase in favorable outcomes in the study group as compared with oral nimodipine, though the safety profile was acceptable.[72] This proves the challenges of replication of results of animal studies to human trials, which puts money and time both at stake.

The impaired cerebrospinal fluid circulation and delayed clearance of the blood after SAH possibly play an important role in the development of DCI.[73] The glymphatic dysfunction results in impaired clearing of brain metabolites, which can accentuate DCI. The role of intraventricular fibrinolysis (IVF) has been studied in several trials with mixed results. A phase III RCT has been planned to compare IVF versus EVD alone in aSAH, to see whether it improves the outcome of patients.[74] The trials of various therapeutics like erythropoietin, magnesium, progesterone, clazosentan, and hypothermia have failed in clinical trials. While milrinone has shown to hold promise, the quality of evidence still needs to be strengthened. The need for a therapeutic agent that can affect multiple molecular pathways to prevent or treat DCI is still unfulfilled. This preclinical to clinical divide needs to be understood and bidirectional TR should be emphasized upon to develop prognostic and therapeutic measures to improve outcomes after aSAH.

Translational Precision Medicine

The focus of medical care is now shifting from evidence-based medicine to a more patient-centric approach. The development of reliable preclinical study models is essential for successful research. The generation of genetically engineered animals is a step forward where effort is being taken to design animal models which can replicate the variability observed in human cohorts.[75] The incorporation of information attained from multi-omics and various biomarkers into patient care requires the integration of this information to define the best management strategy. The concept of *translational precision medicine* includes forward translation, i.e., from bench to bedside, backward translation or reverse translation, using multi-omics to define disease endotypes, digital and molecular biomarkers, artificial intelligence-based data analysis, and patient-tailored companion diagnostics for implementation of precision medicine.[76]

To conclude, successful replication of results found in experimental studies to clinical use in patients with ABI is still afar. The need is to choose a correct animal model, adhering to the rules for maintaining the quality of research in animal studies, assessing meaningful outcomes, carrying out systematic reviews and meta-analysis of animal studies before proceeding to clinical trials, and utilizing both forward and reverse genomic translation to the best of our advantage. The multidisciplinary approach may help to design meaningful trials which might help in improving replication of results in human trials. Although challenging at this stage, the advent of translational precision medicine will help the integration of mechanism-centric translational medicine and patient-centric precision medicine.

Conflict of Interest
None declared.

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