## Commentary

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# Unsolved Problems of Brain Trauma

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### Historical Vignette

Sir Graham Teasdale, an old friend of mine, whose name as a neurotraumatologist has been immortalized by his epoch making study universally associated with the Glasgow Coma Scale (GCS).[1] He is credited with the establishment of the European Brain Injury Consortium and the International Neurotrauma Society, apart from his major contribution to the field of neurotraumatology.[2] Even 40 years later, the evidence showcases the GCS has stood the test of time.[3] My own interest in the field of neurotraumatology dates back to the days with Prof. Kristiansen, my mentor, who was deeply concerned regarding the challenges faced as early as 1949.[4] However, in spite of all the efforts and recent advances, some of the basic issues regarding the management of severe head injuries (SHI) remain unsolved. The list of such problems is long and hence I chose to restrict myself to explore, "Why in spite of all researches—basic and clinical—there has been no or little improvement in the morbidity and mortality following "Severe Head Injury"? This problem remained a subject of study throughout my professional career and even much later. I am reminded of a thought provoking statement by Sir Graham "Nemo satis sapit: nobody knows enough alone."[2] I would like to share some excerpts from the Sir Graham Teasdale oration, I had delivered at AIIMS Neurotrauma conference, New Delhi, 2018 and also the thoughts of renowned neurotraumatologists on the subject.[5-8]

However, first-hand study of a large number of SHI patients brought these problems in sharp focus.[9] The results of this study published as a monograph attracted an annotation in Lancet—"The treatment of the SHI is clearly becoming less the province of the inactive master than it has been hitherto."

One of the important lessons learnt was the need for early angiography and appropriate surgery rather than "patients, watch full expectancy" followed by multiple burr-holes (some called it wood-pecker surgery) if clinical deterioration (dilating pupil, deepening, unconsciousness, developing neurological deficit) set in. Following some such regimes, Jennett, Teasdale, Galbraith *et al*. (1977) reported the mortality of severe head injury to be 51%.[10] Even much higher mortality was reported for some specific subgroups like an acute subdural hematoma or intracerebral hematoma (80–90%)[11-14] [Table 1].

Langfitt reiterated, but none of the (Currently Advocated) modalities have been demonstrated to be effective, alone or in combination with others, by the only acceptable criteria for success, namely, a reduction in mortality or morbidity compared to a comparable group of patients who did not receive the treatment.[15] Langfitt and Gennarelli (1982) wondered, "Can the outcome from head injury be improved."[16]

### The Dawn of the New "Aggressive Therapy"

It was around the 1970s that a number of neurosurgeons experimented with new therapeutic regimes to lower the mortality of SHI (GCS = <8). This was called "Aggressive treatment" consisting of intubation, artificial ventilation, intracranial pressure monitoring, high doses of corticosteroids, barbiturates[17-20] [Figure 1]. Thus, Gordan 1976 authoritatively advocated "There should be no discussion, however, about the necessity in cases of unconscious head injured patients, of the establishment of an artificial airway and controlled hyperventilation before any other measures, diagnostic or operative, are started."[17]

A large multicentric study was initiated in the USA to evaluate this regime. My friend John Jane from Charlottesville, Virginia, USA who was part of this study, during his visit with us reviewed our study on such patients who were



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not submitted to the so-called "aggressive study." Results of our studies were compared and published.[21]

It revealed no significant difference in outcome except for a small group of such patients [Figure 2].

The so-called "Aggressive" treatment failed to provide additional benefits compared to conventional management.

We reported data collected prospectively on 551 cases in Delhi and 822 cases in Charlottesville, Virginia, USA. There was no statistically different mortality rate at the two centers even though the management strategy was different. Somewhat modified "Aggressive" treatment was used in Charlottesville, while the patients at Delhi received none of it—no artificial ventilator, ICP monitoring, corticosteroids, or barbiturates.[21]

A more detailed review of the literature and analysis of a larger series of head-injured patients at our center published in 1986 confirmed these observations. Notwithstanding recent advances, mortality from SHI remained high. New "Aggressive" management strategies (described above) introduced by high expectations in end results.[22]

A number of papers from other centers expressed similar concerns. "But none of the (Currently Advocated) modalities have been demonstrated to be effective, alone or in combination with others, by the only acceptable criteria for success, namely, a reduction in mortality or morbidity compared to a comparable group of patients who did not receive the treatment.[23]

Although conclusive evidence from randomized trials are not available to assess the merits of "Aggressive" treatment as a whole, a survey of the recent literature suggest that reports not finding "Aggressive" treatment to be beneficial are more reliable in comparing series than are those that claim improved outcome.[24]

"Notwithstanding some marginal gains, the mortality and morbidity of SHIs remain unacceptably high. Most neurological centers, especially those interested in Neurotraumatology, continue to report a mortality of 30–50% and even more for patients admitted with GCS<8 even now.[25-27]

"Despite promising pre-clinical data, most trials that have been performed in recent years have failed to demonstrate any significant improvement in the outcome."[28]

NINDS Workshop involving virtually who is of Neurotrauma research acknowledged, "The lack of clinical benefits for any of these therapeutic measures either singly or in combination." The measures included the use of corticosteroid, barbiturates, ICP monitoring, hyperventilation, hypothermia.

"Despite claims to the contrary, no clear decrease in traumatic brain injuries (TBI)-related mortality, or an improvement in the overall outcome has been observed over the past two decades.[29] Reviewing progress in the management of severe head injury between 1960 and 1995, I came to the conclusion that, "In spite of the innumerable clinical, pathological and experimental studies the ideal management of TBI remains an elusive goal."

Furthermore, "In this era of evidence-based medicine, most reports on therapy of these patients fail to stand up to the rigours of the scientific scrutiny. Controlled randomized or double-blind trials are conspicuous by their absence."[30]

Steroids (19RCTs) sample size 10,008 provides strong evidence that using steroids in all patients with TBI is harmful.

Hypothermia: one robust RCT showed worse outcome in patients treated with hypothermia titrated to ICP control.

Surgery: Three robust RCTs (Decompressive Craniectomy) conflicting findings (DECRA Trial), (STITCH trial-closed prematurely) and RESCUE ICP trial.[31-33]

**Table 1: Mortality in severe head injury**

| Author | Series | No. of cases | Mortality rate (%) |
|---|---|---|---|
| Jennett *et al.* 1977 | Three countries: Glassgow, Netherland, Los Angeles | 700 | 51 |
| Jennett *et al.* 1979 | Three countries: Glassgow, Netherland, Los Angeles | 1000 | 49 |
| Becker *et al.* 1977 | Richmond, USA | 160 | 32 |
| Miller *et al.* 1981 | Richmond, USA | 158 | 40 |
| Marshall *et al.* 1979 | San Diego, USA | 100 | 28 |
| Pazzaglia *et al.* 1975 | Bologna, Italy | 282 | 49 |
| Urazzi *et al.* 1984 | Verona, Italy | 1000 | 45 |
| Present series, 1985 | New Delhi | 255 | 43 |

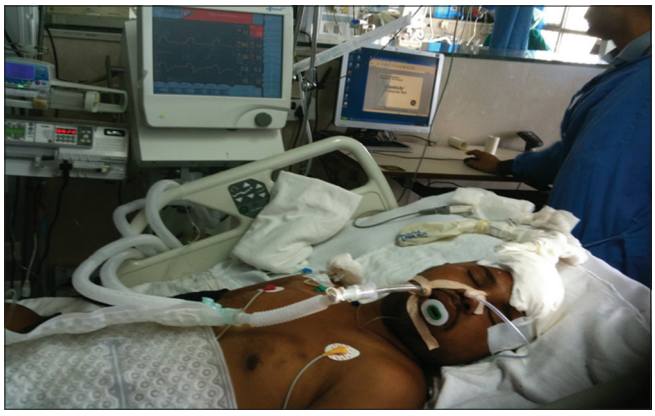

**Figure 1:** SHI patient treated in ICU setup in the current era: Mechanical Ventilation, Sedation, Intracranial pressure monitoring

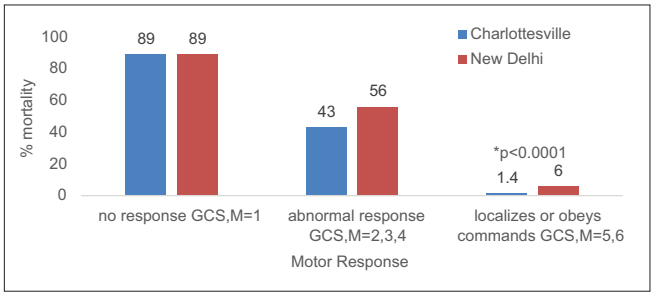


**Figure 2:** Mortality following SHI: Comparison of two series with radically different treatment protocols

"Despite the considerable investment of resources and efforts in producing 191 completed RCTs, very little translatable evidence has been generated".[34]

The results of a systematic review of TBI mortality over the past 150 years suggested that improvements in the clinical management of severe TBI have reduced case fatality rates by more than 50%. However, case fatality rates appeared to have stagnated over the past 25 years.

Stein *et al*: J Neurotrauma 2010 confirmed by Rosenfield *et al*. Lancet 2012.[34-36]

Moderate to severe brain injury (TBI) remains a major global challenge, with rising incidence, unchanging, mortality and lifelong impairment (Based on 191 RTs, enrolled 35, 340 participants).[37]

Seizures prophylaxis: Increasing trends to move away from phenytoin to newer agents (no idea of indications, duration).

This is not to say that there have not been any gains in overall care and outcome of the unfortunate victims of head trauma during those years. The introduction of ambulances fully equipped and staffed hospitals; primary care by a neurosurgical team on arrival there have proved beneficial in reducing mortality and morbidity.

## Therapy Based on Knowledge Derived from Molecular Biology Investigations

Based on recent knowledge gained from investigations on experimental models of head injury using molecular biology techniques, raised hopes for improving the outcome of treatment of brain injuries.[38-41]

"Attempts to investigate the molecular basis of the patho-physiology revealed the insult caused by excitotoxic substances, free radicals, and other secondary metabolites of tissue damage released following the original insult" [Figure 3].

"Therapeutics agents targeted to counter these, found to be useful in experimental animal models of head injury have not proved their utility in human beings."[22]

To date, no clinical data are available, but more data are needed for rigorous documentation of an equivocal effect of therapeutic intervention in experimental studies before human studies will be appropriate. We believe that clinical application or manipulation of oxygen free radical scavengers will have a major role in a powerful therapeutic strategy for brain injury and brain edema in the near future.

There is an urgent need to investigate the causes of failure of neuroprotective therapies in improving the outcome of SHI. I am not aware of any ongoing experimental studies on a hypothesis based prospective clinical studies or protocol-based multi-centric therapeutic trials ongoing in the country. Yet we have today adequate expertise and facilities to undertake such studies. These may not only solve some specific problems of relevance to our country but lead to international standard studies.

To the best of the authors' knowledge so far, no reliable information is available on the beneficial role of therapy based on this knowledge.[42,43]

## Vascular Changes following Head Injury

There has been enough pathological and clinical evidence to indicate the high incidence of cerebral circulatory abnormalities associated with a severe head injury. These include cerebral ischemia, focal vascular spasm, abnormality of cerebral perfusion.[44-49] Notwithstanding this useful information of the pathogenesis of secondary brain damage following injury, no doubt an important factor influencing the outcome has not yet led to improved therapeutic strategy.

## Neuroinflammation following Traumatic Brain Injury

It is now common knowledge that neuroinflammation is a common denominator of diverse neurological diseases not only of infective origin but even others like trauma, ischemia, tumors, and degeneration. It is not just a response to the basic insult, but in many instances, it is responsible for augmenting and perpetuating the disease.[50-53] In addition to its contribution to the pathology in the acute phase, it is now established that inflammation and white matter degeneration persist for years after a single brain injury.[54,55] The possible role of anti-inflammatory drugs in ameliorating the post-traumatic pathology and consequently the outcome remain unexplored.

## The Chronic and Evolving Neurological Consequences of TBI

Recognition of this new entity following TBI, which I have called the IV$^{th}$ Accident raises a number of unanswered questions.

- What is the incidence of Dementia, chronic traumatic encephalopathy, Parkinson's disease, late stroke following mild, moderate, severe; single or multiple TBI?
- What is its patho-physiology?
- Is it only secondary to persistent inflammation?
- Will prophylactic use of anti-inflammatory prevent their evolution?

## Post-Traumatic Epilepsy

- One of the most well-known and studied entity, developing as a consequence of TBI is post-traumatic epilepsy.

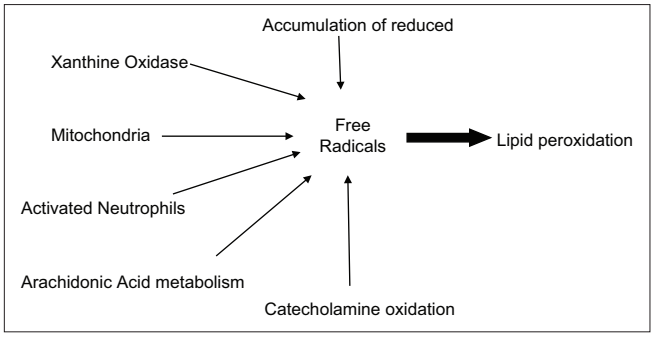


**Figure 3:** Molecular basis of Traumatic brain injury

Notwithstanding nearly a century of knowledge about this entity, there is still no consensus about:

- Its precise pathogenesis
- The indications for prophylactic use of anti-epileptic use of anti-epileptic drugs, which one for how-long?

### Surgery for intracranial haematomas

The traditional multiple burr-hole explorations for diagnosis and management of post-traumatic hematomas, particularly the acute subdural, was already challenged in the 1960s.[9] The same study pointed out that the thin layer of subdural blood associated with brain contusions or intracerebral haematoma was in itself innocuous. Its drainage through burr-holes did not provide relief unless the associated parenchymatous lesion was attended to. Over the years, we confirmed this observation and outlined its surgical management. Commonly the associated parenchymatous lesion was in the temporal lobe. We advocated the removal of the contused lacerated area and the associated intracerebral haematoma along with anterior temporal lobectomy as the treatment of choice.[45] This reduced the mortality of the so-called acute subdural hematoma and the associated parenchymatous lesion to around 40%. In addition, it virtually avoided the need for decompressive craniectomy.[56]

### Decompressive craniectomy

Initially advocated by Ransohoff *et al*. in 1971[57] and Morantz *et al*. (1973),[58] decompressive craniectomy for management of medically unresponsive raised intracranial pressure associated with a SHI was virtually given up as a reliable therapy. It was witnessed a revival in recent years and has been a subject of several multicentric trials.

- The DECRA (Decompressive Craniectomy Trial, 2011)[31]
- The RESCUEicp (Randomized Evaluation of Surgery with Craniectomy for uncontrollable Elevation of Intracranial pressure trial, 2016)[33]
- The STITCH (Trauma): Surgical Trial in Traumatic Intracranial Haemorrhage 2015[32]
- CHIRAG (Collaborative Head Injury and Guidelines Adherence and Outcomes Study) 2016[59]
- CENTER-TBI (Comparative Effectiveness Research): Collaborative European Neuro Trauma Effectiveness Research in TBI 2015.[60]

## Summarizing

Currently, the most debated question regarding surgery relates to decompressive craniectomy, because of the conflicting results of all the existing trials. International guidelines for surgical treatment are not supported by strong evidence. There are considerable uncertainty and debate about which subgroups of patients might benefit most from some types of surgery and the optimum timing of surgery.[34]

- **Steroids (19RCTs) sample size 10,008 – provides strong evidence that using steroids in all comers with TBI is harmful**
- Hypothermia one robust RCT showed worse outcome in patients treated with hypothermia titrated to ICP control[61]
- Surgery 3 robust RCTs (Decompressive Craniectomy) conflicting findings (DECRA trial), (STITCH trial-closed prematurely)
- "Despite the considerable investment of resources and efforts in producing 191 completed RCTs, very little translatable evidence has been generated".[34]

## The Big Question Still Remains

- This is not to say that there have not been any gains in overall care and outcome of the unfortunate victims of head trauma during these years. The introduction of ambulances, fully equipped for prompt resuscitation at the site of accident; quick, medically supervised transport to fully equipped and staffed hospitals; primary care by the neurosurgical team on arrival there have proved to reduce mortality and morbidity
- Similarly, prompt diagnosis of the extent and nature of intracranial pathology using CT Scan has been a major gain Notwithstanding all this, the important question remains, "Where do we go from here?"—Tandon 1994
- Although efforts to develop evidence-based guidelines for routine use in the ICU are a step in the right direction, this one-size-fits-all approach ignores the complex clinical and mechanistic heterogeneity of TBI—Stocchetti *et al*. 2017.

## Where Do We Go from Here?

While the currently ongoing international studies may reveal new evidence to provide better guidelines, like a true detective, is it time to go back to the tell-table evidence provided by pathological studies? Relook at the precious pathology archive of Prof Hume Adams and additional material obtained from the autopsies of the unfortunate failures of the current therapies.

## Conclusion

On the basis of personal experience with management of SHI and extensive review of the literature, it is obvious that in spite of revived interest on the subject there still remain a large number of unsolved problems. This presentation has highlighted only some of these. While lots need to learn about the molecular basis of the pathology, the pathogenesis of associate vascular disturbances and brain edema the possible role of genetic factors and the reason for the failure of therapeutic leads obtained from animal experiments in clinical practice.

To date, no clinical data are available, but more data are needed for rigorous documentation of an unequivocal effect of therapeutic intervention in experimental studies before human studies will be appropriate. We believe that clinical application or manipulation of oxygen free radical scavengers will have a major role in a powerful therapeutic strategy for brain injury and brain edema in the near future.

However, ultimately the most important question remains. The biggest unsolved problem of brain trauma; Is why in spite of all researches, Basic and Clinical, there has been no/little improvement in the morbidity and mortality following "Severe Head Injury"?

"Notwithstanding recent advances in 'aggressive' management of severely head-injured patients, the overall mortality and morbidity remain unacceptably high." The results of a systematic review of TBI mortality over the past 150 years

suggested that improvements in the clinical management of severe TBI have reduced case fatality rates by more than 50%.

However, case fatality rates appeared to have stagnated over the past 25 years.

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**Conflicts of interest**

There are no conflicts of interest.

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