# RESEARCH, INNOVATIONS AND NEW TECHNOLOGIES

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## EPIDEMIOLOGICAL FACTORS ASSOCIATED WITH POSITIVE RECOVERY IN PERSONS WITH SEVERE AND MODERATE TRAUMATIC BRAIN INJURY (TBI)

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Objectives:

1. To review and evaluate the epidemiological evidence on the prognostic or predictive quality of pre-hospital, hospital and post discharge factors on positive outcomes following TBI.

**Description:** Epidemiology involves the search for the foundations of the non-random distribution of TBI in populations. Whereas we have good information on environments and features of people that place them at high risk of injury occurrence, we have less reliable information on factors that influence outcomes following injury, especially those that may control positive recovery. Thus, there is continuing interest by researchers in identifying factors that predict positive outcomes.
One of the most consistent epidemiological observations in studies of TBI is that, in serious brain injury, some patients survive and have normal or near normal recovery while others with similar injuries do not achieve recovery.

**Methods:** The literature on TBI of the past two or three decades is extensive and many papers have addressed questions of prognosis and factors that are predictive of a good outcome. This literature will be searched for epidemiological evidence of prognostic quality, namely, research papers with good internal and external validity.

Prognostic factors may be grouped into four general classes following the pattern of the natural history of TBI: 1) This class includes factors intrinsic to the individual and are non-mutable such as age, gender, race, and genetic composition. These factors unfortunately are not alterable but can provide important insights into the underlying physiological or biochemical processes of human response to brain trauma. 2) In this class are factors that are extrinsic to the individual but can influence outcome following TBI including alcohol use, the external causes of injury and existing injury co-morbidity. These factors are changeable and subject to intervention. 3) This group of factors include those connected with pre-hospital, emergency department, surgical or ICU care and are currently the subject of intense study since the greatest potential for recovery may rest with advances in treatment. 4) This class of factors deal with all elements of post acute care and represent all efforts at short and long term rehabilitation as well as family and community support and organization.

This brief presentation will focus on data that address the first and second of these groups of factors.

## THE BURDEN AND IMPACT OF TRAUMATIC BRAIN INJURIES IN DEVELOPING COUNTRIES: STRATEGIES FOR PREVENTION

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**INTRODUCTION:**

Developing countries are passing through a significant phase of socio-demographic, economic and epidemiological transition with rapid changes in health problems across communities. Restructuring of National Health policies and health care delivery programmes has resulted in a significant decline of maternal and infectious diseases. The near eradication of poliomyelitis is a classical example of this changing phenomena. At the same time, these countries are also witnessing significant changes in terms of population growth, urbanisation, motorization, industrialisation; market oriented economic liberalisation, migration from rural to urban areas and growth in technological spheres. The massive impact of media with changing life styles has added a new dimension to the existing socio-economic problems. A consequent effect of these changes has been the emergence of the double burden with both communicable and non-communicable diseases taking a heavy toll in these communities. In order to effectively meet these new challenges, health services have not efficiently geared up due to limitations of manpower, technical limitations and deficient resources (1, 2). The ratio of doctors to population and availability of health care resources are abysmally low compared with developing countries.

This emergence of double burden of diseases has resulted in bringing injuries to the forefront of health care delivery system. As per the available data, it is acknowledged that injuries are one among the five leading causes of mortality, one among the 10 leading causes of morbidity and contribute for nearly 20-30% of totally disability. As per the Global Burden of Diseases study report, injuries specially road accidents, will be the 3rd leading public health problem in developing countries (3). Among the different types of injuries, Traumatic Brain Injuries (TBIs) afflict significant number of individuals contributing for mortality, morbidity, disability and socio-economic impact. The burden and impact on the individual, family and developing societies are significant from all angles. In India, injuries are the 7th leading cause of death and nearly 10 million people are injured due to injuries. Epidemiological understanding is crucial to design, implement and evaluate interventions in terms of affordability, cost effectiveness and culture specificity.

The present report examines the problem of TBIs in developing countries in its various dimensions (magnitude of the problem, risk factors (role of alcohol) external causes, survival and outcome). Further, solutions likely to have a positive impact towards prevention are highlighted.

**THE BURDEN OF TBIs:**

The information gap from developing countries is most obvious, as there are few published population based studies in the region. Many of the health care systems do not include TBIs as a reportable and notifiable condition. Even information on injuries is deficient in most of the countries. The extent of hospital registration due to TBI varies widely based on hospital policies, availability of facilities and the referral pattern from some of the available literature. It is estimated that nearly 10-40% of emergency room admissions and surgical wards is constituted by TBIs. The incidence of TBI varies from 160-670 / 100,000 population per year. This wide variation in incidence stage is contributed to inclusion and exclusion criteria, case definitions, and source of case identification and variations in classification methods (4-7). The global incidence of TBIs as per World Health Organisation (WHO) is estimated to be 200/100,000 (8). Given the bias in reporting of TBIs, the problem appears to be much higher in developing countries. Mortality from TBIs varies from 20-120/100,000 per year with global estimates of 20/100,000. Information on the prevalence of TBIs is not known for any country in the developing world except the study from Bangalore revealing the presence of TBI to be around 320/100,000 population (9). The case fatality rates vary from 5-30% with the global estimates being around 10%.

**AT RISK POPULATION:**

The age-sex distribution of TBI hospitalised subjects reveal that male to female ratio is in the range of 4:1. Almost all the studies confirm to the fact that TBIs increase from childhood ages, reaches the peak at 20-29 years and declines around 4th decade, with a consequent increase in the elderly population. The occurrence of TBI is influenced by a number of factors like age-sex distribution of the population, extent of technological progress, role of external causes, safety priorities and, prevention and safety policies. The extent of alcohol consumption varies from 20-70% in different studies. Recent reports have highlighted the increasing occurrence of alcohol consumption among persons with TBI.

**EXTERNAL CAUSES:**

Several similarities and differences are noticed in the causation of TBI in developed and developing regions of the world. Road traffic injuries (RTIs) continue to be the leading cause followed by falls and violence to the extent of 50-60%, 15-25% and 10-15% respectively. Other significant causes are work-related injuries, sports injuries, and fall of objects and disasters. Road traffic injuries (RTIs) account for 60-70% of TBIs in developing countries. With nearly 1,00,000 deaths and 10 million injured people in India alone, RTIs are the leading cause of deaths and disability with significant socio-economic losses. The Global Road safety Programme estimates reveal that in the next 10 years, 6 million deaths and 60 million injuries are likely to occur in developing countries with more than one third having a TBI (10). In majority of these countries, the vulnerable road users are pedestrians (30-40%), two wheeler occupants (35-45%), pedal cyclists (10%) and passengers in heavy vehicles (20%) (4-

7,11,12). Significant differences are observed in urban and rural areas depending on the motorization pattern.

Nearly 70% of falls occur at homes due to personal and environmental factors. Children and elderly are injured more in sharp contrast to road traffic injures. Violence due to a number of personal, political, social, communal and religious problems is on the increase in all developing countries. The recent recognition of violence as a public health problem has given rise to its increasing role in injury related mortality and morbidity. The epidemiology of violence and TBI has not been investigated in greater detail and preventive efforts are at cross roads. The regional variations in violence with some countries (South Africa, Sri Lanka, others) is often attributed to socio-political anarchy in these countries.

**EMERGENCY AND PRE-HOSPITAL CARE:**

A recent review of the studies of emergency and prehospital care in developing countries has identified several critical issues resulting in delay and negative prognosis among injured persons. In contrast to developed countries, the availability of first aid at or near to injury site, delays in transportation of patients from injury site to nearest hospital, absence of a triage in referral systems and, delayed time interval in reaching a definitive hospital are major problems in emergency and prehospital care. Further, lack of communication facilities, limited availability of ambulance services, lack of facilities in individual hospitals and required diagnostic services accentuate the problem. Some of the recent studies from India have highlighted that only less than 20% of patients reach a hospital within one hour and more than 60% beyond 3 hours (4,13). Lack of emergency care for persons with brain injury will result in increasing the severity of injuries, thus leading to higher proportion of deaths and disabilities.

**SEVERITY OF TBI:**

One of the major determinants in survival and outcome from TBI is the severity as measured by Glasgow coma scale. Selected studies reveal that 70-80% are mild TBIs, 10-20% of moderate and 10% of severe in nature. The presence of skull fracture has been noticed in 5-10% of brain injured persons.

**DISABILITIES AND IMPACT OF BRAIN INJURY:**

Information on this particular aspect has been very limited from developing countries due to the lack of follow up and outcome studies. A recent study from Taiwan revealed that adequate recovery at hospital discharge was noticed in 80% of subjects, moderate disability persisted in 8% and 1% remained in permanent vegetative stage. In Bangalore, it was noticed that nearly 48% of discharged subjects had disabilities affecting all areas of life. Recent literature reveals that even mild brain injuries with a GCS of more than 13 results in long term psychosocial disabilities. Among various types of disabilities, activities of daily living, information processing skills, memory, speech, cognitive abilities and activities in social spheres of life were affected to a

greater extent, thus diminishing the quality of life (14).

**STRATEGIES FOR PREVENTION:**

It is increasingly recognised that TBIs are a silent hidden and unrecognised epidemic. With much of the health care resources being spent on communicable and infectious diseases, there is a paucity of manpower and resources to meet the challenge of TBI prevention. Several major problems faced need to be addressed to save lives at an early stage. Some of the known strategies likely to yield positive results are establishing systems to develop epidemiological surveillance, co-ordinated and integrated approaches, strengthening emergency and pre hospital care, and development of national policies and programmes. Several well established and time tested strategies like promoting helmet usage, reducing drunken driving, speed control methods, and good road safety practices, safer roads and vehicles will undoubtedly yield positive results. National commitments, safe transfer of technology and strengthening infrastructure would result in reducing the burden of TBIs in developing countries.

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## BRAIN DAMAGE AND THEORIES OF RECOVERY: CURRENT CONCEPTS AND IMPLICATIONS FOR TREATMENT

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There is currently no universally accepted definition of functional recovery from brain injury and this stems, in part, from the difficulty in defining the underlying, physiological mechanisms of recovery. Brain injury itself represents a complex cascade of events that unfold over hours to months after the initial, precipitating incident. Different theories and descriptive observations have been used to explain and account for the varying degrees of recovery that occur after TBI; often with no relation to one another. New technologies provide important analytical power, but are sometimes employed to support highly simplified and unrealistic views of nervous system organization. My presentation will address some of these issues in historical context, and describe several of the more current hypotheses used to 'explain' how functional recovery occurs after TBI. I will try to highlight what mechanisms might underlie behavioral compensation, restitution and substitution of function following brain damage. The concepts of redundancy and multiple representations of function will also be examined along with more structural changes underlying "plasticity" such as unmasking of synapses, diaschisis, and sprouting and regeneration. I will briefly present some new experimental data to show that neurosteroids, like progesterone may be used as post-injury treatment to improve functional and morphological outcomes.

## INNOVATIONS IN NEUROINTENSIVE CARE: OLD DREAMS AND NEW CHALLENGES COMING TRUE

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**Background**

A better understanding of the quality of care possible today for patients with acute traumatic brain injury may be given by considering how many progresses have been made. While the early diagnosis and evacuation of intracranial space occupying lesions has long been the main focus in the neurosurgical management of head injuries, the management itself has changed considerably. Fifty years ago the possibility of measuring intracranial pressure was more a sophisticated investigational method than a clinically applicable methodology (8). Today such monitoring is advocated as part of the "minimum standard of care" required for every severely injured patient (2).

The concept that intensive medical treatment could improve outcome arose forty years ago. Airway protection and supported ventilation for the severely head-injured patients were proposed by pioneers (10, 5, 7) and the spectrum of care was extended from inside the hospital to the accident scene. Attempts were made to rescue trauma patients in a standardized way, to refer them to appropriate facilities and to concentrate on them both surgical and medical resources in a timely fashion. Nobody seriously questions the fact that severe head injured patients require intensive care, aggressive monitoring and early rehabilitation. When this level of care is not offered to every patient in the western countries, that is perceived as an inadequacy of care (3, 2).

An outstanding cultural change has undoubtedly taken place.

**An old dream: Intensive care for the severe head injured patient**

In the USA, Becker et al. (1) suggested that early surgery combined with ICP monitoring and aggressive therapy could improve outcome after head injury. The central role of raised intracranial pressure was identified, and ICP measurement and control became part of the management. Since cerebral perfusion was recognised as the main goal of treatment, preservation of cerebral perfusion pressure (CPP) along with maintaining systemic status, became accepted endpoints. These approaches have been increasingly applied in the last decade and, although proof of their benefit is lacking, they are included in authoritative guidelines, produced on an evidence-based approach or by expert consensus (2, 9).

**A perspective: make ICU available to all patients in need**

Nevertheless, many head-injured patients are managed in Intensive Care Units, studies

confirm that there are still marked variations within a centre and between centres (4, 11, 6, 12). Data from the European Brain Injury Consortium prove that ICP monitoring is used in a proportion of eligible patients varying from 0 to 70%.
A way for making old dreams come true is to extend ICU access to all patients, or at least to a greater proportion of patients, who may benefit from it.

**A new dream: continuous cerebral exploration at the bedside**

Since the brain is contained in the skull, only the advent of the CTScan has allowed a simple, repeatable exploration of the intracranial space for clinical purposes. Early surgery of intracranial masses, surveillance of non-surgical lesions, definition of parenchymal and vascular damage became possible and are now routine. The brain function is much more complex than revealed by the CTScan findings, and new imaging techniques, as NMR or PET, offer information on many aspect of cerebral physiology and pathophysiology. All imaging techniques, as long as portable CT will not be widely used, have the limitation of requiring the patient to be moved. Continuous imaging is, moreover, not possible, and the possibility of frequent, systematic control is offered only by new monitoring techniques, such as cerebral extraction of oxygen, cortical oxygen tension or microdyalisis.

**New challenges**

The application of new technology and an extended use of what is already validated represent an exciting perspective. However the use of increasingly sophisticated equipment, as well as a wider use of intensive care, may increase costs and raise the question of what is really going to benefit patient and society. The answer to all these challenges requires more research. Useful innovation may only derive from knowledge.

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## RESEARCH AND NEW TECHNOLOGIES IN REHABILITATION

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Recently, advances in various fields of technology have been achieved which are of increasing importance for the rehabilitation of patients with brain damage. There are e.g. advances in neuropharmacology, brain imaging and especially in IT - most pertinent to rehabilitation. The paper focuses on teletherapy/telerehabilitation as a form of rehabilitation which can complement and extend in- and outpatient rehabilitation programs and reach the patient in his home even in remote areas.
Traditionally, patients with brain damage undergo inpatient rehabilitation (IR) programs followed by community based outpatient rehabilitation (OR). In order to improve outpatient rehabilitation for patients who are faced with transportation problems or have no access to adequate rehabilitation resources (e.g. living in remote areas) the goal of the present study was to test off the shelf available communication and computer technology as a means of neurological rehabilitation over long distances (technical feasibility study). In addition, we explored which functional disturbances after brain damage are appropriate for teletherapy (TT) (indication profile) and whether patients accept this type of indirect, but personal therapy medium (compliance).

**Method:** Conventional IBM compatible Personal Computers were used together with windows and Proshare‰, a special program by INTEL which allows application sharing under videoconferencing conditions. Conventional ISDN telephone lines were used to connect two computers for interactive communication. Under this technical scenario a patient and a therapist can communicate vis-à-vis seeing and hearing each other and sharing their applications on the computer. I.e. the therapist can interact with the patient as if the patient was present. He can load a therapy program on to the patient's computer, see how the patient is responding and intervene directly into what the patient is doing on his computer. If the patient is to produce coherent text, e.g. in WinWord, the therapist can start the programs on the patient's computer, open a file, write into the file to provide him with material and guide/correct the patient's activity.
20 patients with damage to the central nervous system volunteered in the study. They had suffered from cerebral infarcts, hemorrhages, head trauma or encephalitis and were recruited by the rehabilitation doctor responsible for the TT-program and the TT-team. Relatives were also contacted and informed about the project. Patients underwent 4 weeks of teletherapy (TT) in the rehabilitation hospital (in addition to conventional therapy) and 8 weeks under home conditions. Per day 3 TT sessions were provided. During the hospital phase patients were acquainted with the computer

and the handling of Proshare. The same therapist who performed inhouse therapy also continued home teletherapy to ensure constant patient/therapist relationships.

**Results:** The major goal of the study, i.e. technical feasibility, could be achieved. It could be shown that conventional computer and telephone (ISDN) technology are sufficient to provide the technical basis for interactive long distance therapy in an home environment (home teletherapy). Even if patients did not have computer proficiency at the onset of the project they accepted teletherapy as a therapeutic medium and were willing and able to become computer and Proshare competent and to endure three months of continuous daily therapy sessions. It turned out that various cognitive disturbances such as aphasia, agraphia, alexia, acalculia, attention, concentration and memory deficits, visuospatial and constructional problems and some cases of dysarthria, and fine manumotor deficits could be approached by means of TT even in patients with severe motor problems. Patients who are going to be reintegrated into work can be supported at their work place.

**Discussion and conclusion:** TT in neurological rehabilitation appears to be a valuable tool to extend inpatient rehabilitation into the home or work domain and to assist their reintegration. It provides patients with rehabilitation facilities who otherwise would not be able to participate in outpatient rehabilitation programs. Neurocognitive disturbances are the major domain of teletherapeutic interventions including vocational therapy immediately before return to work or during work integration. Supportive tele-psychotherapy and counseling also play a major role in long term adaptation and integration.

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## SELF-ASSEMBLING PEPTIDE SCAFFOLDS FOR BRAIN INJURY REPAIR

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A new type of self-assembling peptide (sapeptide) scaffold hydrogels that serve as substrates for neurite outgrowth and synapse formation has been developed. This peptide-based scaffold is amenable to molecular design, using chemical or biotechnological syntheses. It can be tailored for a variety of applications. The sapeptide scaffold is formed through the spontaneous assembly of ionic self-complementary oligopeptides under physiological conditions, producing a hydrogel material. The scaffold is not only able to support neuronal cell attachment, differentiation as well as extensive neurite outgrowth, but also it is a permissive substrate for functional synapse formation between the attached neurons. Since primary rat neurons form active synapses on such scaffold surfaces *in situ*, it suggests that they could be useful for tissue engineering, neuroengineering and brain injury repair applications. Furthermore these peptide scaffolds did not elicit a measurable immune response nor tissue inflammation when introduced into animals.

The self-assembling sapeptide scaffold hydrogel belongs to a class of biologically inspired materials. The self-assembly event creating the sapeptide scaffold takes place under physiological conditions and they are readily transportable to different environments. These new biological materials will become increasingly important in developing approaches for a wide range of innovative medical technologies. These technologies include controlled drug release, new scaffolds for cell-based therapies, neural tissue engineering and brain injury repair. Combine with stem cell technology, we can anticipate in encapsulating stem cells in the sapeptide scaffold, allowing them to differentiate into desired cell types with specific growth factors and cytokines, and then apply the cell-scaffold systems into needed tissues. These biocompitable and biodegradable peptide scaffold hydrogels developed through molecular self-assembly will likely have a broad range of applications for tissue repair and tissue engineering.

## HYPERBARIC OXYGENATION AND NEUROREHABILITATION FOR PERSONS WITH TBI

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**Statement:**
Following all the gas laws of physics, multiple physiologic effects take place with the use of hyperbaric oxygenation which could possibly suggest it become an integral modality in the treatment of traumatic brain rehabilitation both in the acute and long-term patient. It's ability to correct early and long-term cerebral edema and hypoxia even with compromised circulation as well as its enhancement of plasticity are a few of said attributes.

**Background:**
Over the years there have been approximately 312 traumatic brain injury patients treated with hyperbaric oxygenation ranging in age from seven months to seventy-four years with the time of entry from four weeks to fifteen years and the total number of treatments from ten to 188 sessions ranging from 1.5 to 2.0 ATA, for forty to ninety minutes either once or twice a day. No trials were double blinded. Although a large percentage of the patients responded with some degree of improvement, only seventeen percent returned to normal function, fifty-three percent showed some improvement neurologically, and thirty percent showed no change. Little objective documentation was noted with the exception of one control study presented by Wassmann[1] who used EEG analysis correlating the increased alpha and beta rhythms with a clinical response to therapy. These results in traumatic mid-brain syndrome were highly positive with both a reduction of morbidity and mortality. In an attempted replication, a study was done by Rockswold[2] but the study was flawed primarily with the time of entry and the number of treatments. Mogami and Hayakawa[3] reported some excellent results in reduction in lactate pyruvate and reduction of cerebral edema in the acute injuries. Noting that clinical improvement without scientific documentation could be achieved in even long-term traumatic brain disease with Glasgow Coma Scales as low as 3, Neubauer[4] developed a procedure of utilizing functional imaging before, during and after hyperbaric oxygenation sessions to document the effect. Thus the patient was used at their own control since all modalities of physical therapy, occupational therapy, speech therapy, biofeedback, etc. had been abandoned.

**Materials and Methods:**
Sixty patients with varying degrees of traumatic brain injury, ranging in age from three to eighty years of age with onset of injury from six months to fourteen years were treated with hyperbaric oxygenation in a monoplace Vickers chamber. These patients had Glasgow Coma Scales ranging from 3 to 12. All patients seen had been referred by

other physicians and were told that nothing further could be done. Single photon emission computerized tomography (SPECT) imaging was performed as a baseline, repeated sequentially, and then at the end of the treatments to document the effects of hyperbaric oxygenation on recoverability of the ischemic penumbra. These studies were performed on a single head El-Cint gamma camera with high resolution. The tracers used were HMPAO Technesium 99. In earlier cases Iofetamine 123 was available but more recently Ceretec and Neurolite are being used.

The treatment schedule varied but most patients received one hour at 1.5 ATA from eighty to five hundred consecutive treatments. Patients with seizure disorder were treated between 1.1 and 1.25 ATA and this was not a contraindication to therapy. In certain patients, when leveling off occurred, the pressure was raised to 1.75 ATA. All modalities of physical therapy, occupational therapy, speech therapy, biofeedback, nutritional counseling, acupuncture, and herbal medications when indicated were utilized as part of the program.

**Results:**
In nearly all of the cases the G-tube was removed and in eighty percent of the cases the tracheostomy was closed. These features alone markedly reduced the cost of care. Few with the Glasgow Coma Scales at the lower level ever returned fully to society. In seventy percent of the patients, there appeared to be some degree of improvement to the point of being able to communicate with the family either verbally, word board, computer, or sign language. This was extremely meaningful to the families since many of the patients had either been locked in or in an apollic state for a period of time. Because of time constraints, three representative cases will be presented with clinical data and SPECT imaging. In none of the patients has there been regression after the succession of treatment. Three cases will be presented showing significant improvement with ages at time of injury ranging from three to twenty-six, and total number of treatments from fifty to five-hundred.

**Conclusion:**
Clinical reports throughout the years have been encouraging. A recent article in the Lancet5 suggested that squeezing oxygen through the swollen brain was responsible for the overall improvement in the mortality rate over the past twenty-five years. They however did not refer to hyperbaric oxygenation but this alluded strongly to one of its effects. Hyperbaric oxygenation is known to reduce focal and generalized cerebral edema to correct fully or partially hypoxic areas which may be comprised of dormant idling neurons receiving enough oxygen to exist but not enough to fire electrically for periods up to fourteen years. Re-activation of this zone has been demonstrated with high dose oxygen. In early intervention, it reduces lactate / pyruvate peaks and reduces the stickiness of the white cell to the endothelium and tends to deglutinate platelets. It also furnishes the appropriate $PaO_2$ to the DNA and mitochondria, and protects the blood brain barrier and cell membrane. In long-term use it causes re-vascularization

and enhances debridement with improved PMN function. In addition to all of its other attributes, hyperbaric oxygenation enhances plasticity.

Documentation however is essential by using the same patient as his/her own control. The specific effect of hyperbaric oxygenation on an individual may be documented by changes in flow and metabolism along with clinical observations. Frequently, this makes a significant difference in the patient even when it has been said that nothing further could be done. The reduction in morbidity and mortality and financial burden should not be overlooked.

The ultimate outlook in severe traumatic brain insult depends upon:
1. location and size of the irreparably damaged area
2. size and location of the ischemic penumbra (recoverable brain)
3. organization and reorganization of impaired and non-impaired sensory and motor neurons
4. the degree of asymmetry
5. the decasation at the cord medullary junction.

Edward Teller, Father of the Hydrogen Bomb, has summarized its physiologic effects by stating "*following all the gas laws of physics, hyperbaric oxygenation furnishes free molecular oxygen to the cell for immediate metabolic use without energy exchange even with compromised circulation*" [6].

It is hoped that this presentation will provoke further studies with hyperbaric oxygenation both in the acute and long-term traumatic brain injury patient.

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## RESEARCH ON TBI - CURRENT PLANS AND FUTURE DIRECTIONS

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The incidence of traumatic brain injury in the U.S. is approximately 95 per 100,000. Incidence in European nations varies but is within the same order of magnitude. Ascertainment of the precise number and outcomes for mild traumatic brain injury is especially difficult, because many of these individuals do not present to trauma centers, indeed may not come to medical attention. Thus, ascertainment bias may exist in reported studies.

Recent scientific evidence suggests that careful control of intracranial pressure during acute management of TBI and this appears to be a crucial determinant of outcomes. Despite considerable enthusiasm and a wide variety of successes in animal models, drugs targeted at "neural protection", i.e. drugs that interrupt the cascade of cell death after traumatic brain injury, have to date showed no convincing benefit in human clinical trials. In part this may be because the pharmacokinetics of these agents in humans have not been adequately matched to successful animal models.

Rehabilitation remains a mainstay of treatment for individuals with TBI. However, only a small number of well controlled studies investigating the efficacy of rehabilitation for TBI have been done. Recently, Salazar and colleagues reported on a randomized controlled study of rehabilitation for moderately injured individuals. In their study, individuals receiving inpatient therapy has no better outcomes than those receiving a minimally supervised program at home. However, they did note a trend for more severely injured individuals to benefit from the inpatient program. These data are consonant with findings in individuals with stroke-individuals with more severe strokes appear to gain the greatest benefit from rehabilitation, although their rehabilitation may take considerably longer. In addition, these findings point to the need for studies stratified among individuals with TBI of different severity and sequelae. A wide variety of new therapeutic modalities, e.g. virtual reality, errorless learning, etc. are availabale for clinical evaluation.

Similarly, community integration and vocational retraining programs have demonstrated some evidence to support their efficacy in treating individuals with TBI, although the strength of the evidence is not overwhelming. Certainly, individuals with TBI and their families can attest to ongoing problems and disappointments. Measurement of the real success of such programs is made especially difficult because of confounding issues, e.g. individual motivation, concomitant behavioral difficulties, psychological variation and the level of unemployment. New approaches in this arena, e.g., virtual mentoring, are just beginning to reach the community.

The need for improved treatments for TBI and for comprehensive outcome measures to include all stages of the continuum of care for individuals with TBI has lead the National Center for Medical Rehabilitation Research to issue several research

initiatives. These include a Request for Applications for Pilot Clinical Trials for Pharmacologic Agents in Pediatric Traumatic Brain Injury, Clinical Trial Planning Grants for Pediatric Rehabilitation, Innovative Strategies for Therapeutic Interventions in Rehabilitation and a solicitation for a Clinical Trials Network for TBI. This network will consist of sites linking trauma care, rehabilitation and community outcomes. The intent of this cooperative agreement will be to provide the infrastructure to allow large-scale trials of therapies for TBI throughout the treatment continuum.

## HYPERBARIC OXYGENATION (HBO) IN SEVERE MID-BRAIN INJURY - A RANDOMIZED STUDY

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**Introduction:** Following an acute traumatic brain injury the extent of hypoxia is the most critical factor influencing secondary brain lesions and the survival of neural tissue.
Increased oxygen availability to neuronal tissue using high pressure oxygen in a hyperbaric chamber and improving the cell metabolism and energy state in this critical situation is the root idea of hyperbaric oxygen therapy (HBO). Experimental evidence and clinical trials support the assumption that HBO has a potential effectiveness for traumatic or ischemic lesions of neural tissue.

**Methods:** In experimental studies we ascertained the oxygen tolerance limit of the injured human brain. So we applied HBO at pressures of 1.5 ata with exposure of 45 minutes. Ninety nine patients with mid-brain syndrome after severe head injury were randomized. All patients were treated with the same intensive monitoring and measures (Group A) and every second patient (Group B) received HBO in addition.

**Results:** The survival time was distinct longer and the survival rate significant larger in Group B patients. At the end of the study 74% of Group A patients were dead or apallic as compared to 53% in Group B. Complete recovery occurred in only 6% in Group A, but in 33% of Group B.

**Conclusion:** This study supports the experimental findings of improved outcome by HBO after temporary focal ischemia in middle cerebral artery occlusion in rats. Here also enhanced oxygen supply to marginally perfused cells is assumed. Therefore HBO in severe "energy crisis" of the brain may prevent secondary damage in the penumbra region and contributes to better clinical outcome.

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## DISABILITY CHANGES AFTER INJECTION OF BOTULINUM TOXIN A (BTX–A) ON PATIENTS WITH UPPER LIMB SPASTICITY FOLLOWING TRAUMATIC BRAIN INJURY

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Increased stretch reflexes, abnormal cocontraction and muscular contractures are disorders of muscular tone causing disabilities in brain injury. The treatment of muscular tone disorders in the early phase of rehabilitation could avoid the appearance of tendons and muscles retractions and allow further improvements in physical therapy. The aim of this study was to evaluate the effect of botulinum toxin A ( BTX-A) on patients with upper limb spasticity following traumatic brain injury in the early phase of rehabilitation treatment. **Methods:** Eight patients affected by disorders of muscular tone following severe traumatic brain injury (Glascow Coma Scale = 8 o < di 8 ) with severe spasticity were investigated before and after injection of Botulin toxin. Brain injury occurred not later than one year from the first injection. Patients with severe spasticity were treated with BTXA injection (20-40 units ) under EMG guidance. After injection with BTXA patients were treated with physical therapy and casting. A second dose of BTXA was administered in a range of time from three up to six mounths, as soon as a severe spasticity was going to appear. Outcome Measures were considered modified Ashworth Scale,wrist Range of Movement(ROM), Upper Limb Motricity Index and Motor Functional Indipendence Measure (FIM). **Results:** Adverse effects were not registered. Outcome measures were assessed 4 weeks after the first and second injection of BTXA. The effects of Botox on outcome measures were examined across three levels using a 1-way analysis of variance (ANOVA). Results are summarized on the Table. The investigation evidenced a statistically significant change of spasticity. Self care and mobility improved.

| | Before BTXA | 4 weeks after first injection | 4 weeks after second injection | |
|---|---|---|---|---|
| Modified Ashworth Scale | 2.75 +/- 1.04 | 1.63 +/- 6.52 | 1.13 +/- 0.35 | P=0.000 |
| Motor FIM | 56.13+/- 3.87 | 57.25+/- 3.24 | 58.13 +/-3.40 | P = 0.004 |
| Upper Limb Motricity Index | 16+/- 4.36 | 23 +/- 8.45 | 23 +/- 8.45 | P=0.024 |
| Wrist range of movement | 15.80+/59 | 32.88 +/ 9.73 | 33.50 +/-9.30 | P= 0.000 |

**Discussion:** FIM scores did not change significantly after treatment with BTXA. However, greater facility in nursing care and reduced disability were found in all subjects. Ashworth Scale and Range of movement changed significantly after the treatment with BTXA. An improvement of motricity was registered in patients with residual function in extensor muscles. These dates should suggest that BTX-A treatment is effective in reducing spasticity and range of movement in patients with focal upper limb muscolar tone disorders secondary to traumatic brain injury. In addition, BTXA treatment improves upper limb motricity but poorly influences on aspects of daily functions, as there is a wide variety of factors, that interfere with the outcome. However in the early stage of rehabilitation of traumatic brain injury the treatment with BTXA prevents deformity associated with hypertonicity as the claw hands due to spasticity of flexor muscles.

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