Guest Editorial

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Targeted Therapy: What are the targets?

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INTRODUCTION

The battle against the worldwide epidemic of traumatic brain injury has many fronts. Undoubtedly, the greatest effect of reducing the toll from injury comes first from prevention and then good primary care. For those victims with severe brain injury and who reach Level 1 Trauma Centre, the battle lines are directed towards preventing further injury to an already injured brain. Our understanding of the events which unfold after injury and of the harmful influence of secondary factors, particularly hypoxia and hypotension have increased enormously in recent decades. The CT scan shows the morphology of injury and aids in planning surgical and non-surgical treatment. The awareness since the 1970s of the frequency and significance of hypoxia has focused treatment and a better understanding of evolving diffuse axonal injury and other post-traumatic cellular and subcellular changes gives us new hope for future treatments.

PROTOCOL BASED TREATMENT

In the 1970s, armed with the increasing awareness of the importance of raised intracranial pressure and brain swelling, hypoxia and hypotension, the newly developed capacity for prolonged ventilation in intensive care units was harness to the management of severe brain injury. The key targets for management are intracranial pressure < 25 mm Hg, cerebral perfusion pressure (CPP) > 60 mm Hg and normal oxygenation. Management principles including these targets have not changed significantly in the past thirty years. Not only are the targets limited but the means of treatment are also limited. There is generally a stepwise series of treatments based on assessment of available evidence and applied in sequence to all patients. There are recognized limits to this approach dictated by the known pathology of the injury. These targets are global and injuries are not uniform. There is lack of uniformity between patients. Attempts to target therapies to individuals and to injury types have been discussed frequently.

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TARGETED TREATMENT

In 1989, Dearden and Miller suggested that ICP reduction therapy must be more selective. They proposed selecting hypnotic versus osmotic therapy on the basis of cerain bedside parameters which might indicate whether raised ICP was due to hyperemia, in which case hypnotic therapy was appropriate, or to increased water content, in which case osmotic therapy was appropriate. Other attempts to define individual global targets include the study on comparing CPP versus ICP protocols from Baylor, the use of autoregulatory thresholds determined by transcranial Doppler (TCD) from Cambridge and from their own studies which combined jugular venous oxygen saturation ($sJVO_2$) and TCD. ICP and TCD are easy to measure, robust and have a defined relationship with outcome. They are however surrogate targets for the real treatment targets, cerebral blood flow(CBF) and metabolism. Surrogates do not always accurately define the true target and may lead to over-treatment for example with inotropes or inappropriate ventilation on under-treatment with risk of ischemia.

Standard protocols probably cope with individual variations by relative over perfusion and over oxygenation. Even so appropriate CBF is not only dependent on CPP but also depends on the presence of autoregulation, the normal lower limit of autoregulation for a particular patient and regional flow characteristics particularly regional vascular resistance. Furthermore, the required tissue oxygen level will depend upon the metabolic rate which may be globally reduced after brain injury. Direct measurements by PET scanning can show the range of regional and temporal variations of CBF and metabolism. The ideal monitor might measure CBF and metabolism directly and to be able to identify the vulnerable tissues.

It is possible to gain an index of CBF and metabolism globally by TCD, $sJVO_2$ catheters. It is possible to measure focal CBF by tissue oxygen catheters, NIRS and other techniques. I would like to consider that the claims of tissue oxygen and tissue dialysis measurements as providing valid targets.

WHAT IS A VALID TARGET?

A valid treatment target might have the following properties:

1. It can be measured directly
2. It has a clear relationship to outcome
3. It can be acted upon
4. The action can be shown to improve outcome

Brain tissue oxygen tension in severe brain injury has potential value. The reasons are,

1. The occurrence of brain tissue hypoxia
2. The depth and duration of tissue hypoxia can be shown to be independent predictors of unfavourable outcome and death
3. Brain tissue oxygen can be changed by increasing FIO_2 and by adjusting ventilation

Brain tissue oxygen has a relationship with $sJVO_2$. Not unexpectedly, the tissue oxygen measurements tend to reflect regional brain oxygenation whereas $sJVO_2$ tends to reflect global oxygenation therefore brain tissue measurements and $sJVO_2$ are complimentary. Brain tissue oxygen may be a valid target because:

1. The methodology is robust and minimally invasive
2. It provides continuous measurements
3. It is related to outcome
4. It provides information which is not otherwise available
5. It can be acted upon by increasing perfusion pressure, increasing FIO_2 or changing tissue CO_2.

One of the difficult decisions in applying this methodology is where to measure tissue oxygen – from apparently normal brain which is easier to identify or from apparently injured brain which may be more vulnerable but more variable. It remains to be determined whether focusing on tissue oxygen values will improve outcome.

BRAIN TISSUE DIALYSIS

Tissue dialysis provides much information about the metabolic changes after injury. The substances measured include indicators of metabolism, excitatory amino acids, inflammatory agents and indicators of cell membrane breakdown. The metabolic markers can be shown to be related to outcome. They may be used to determine the lower limit of CPP and hence to direct therapy most effectively. Utilising tissue dialysis with Lund protocol justified reducing CPP to under 50 mm Hg in some patients. Others found that in some patients CPP needed to be at least 70 mm Hg in order to normalize energy markers. Changes in glutamate may indicate an impending state of hypoxia and allow pre-emptive treatment.

Hence, as a source of valid targets dialysis has the following properties:

1. Information is gained from tissue dialysis which can be acted upon
2. Information is not otherwise available
3. Measurements are not continuous and are technically demanding
4. It has yet to be shown whether utilizing the metabolic information available from tissue dialysis males a difference to outcome.

SUMMARY

Therapy can be targeted to individual patients taking into account continuous bedside measurements of TCD and $sJVO_2$. These supplementary methodologies have been available for a decade are still not sufficiently robust for general use. So what new targets might be developed from existing technology? Tissue oxygen measurements has some claims as a useful target but is ultraregional and the most useful region for measurement may not be definable. Dialysis provides unique information but is ultraregional and technically difficult. Until continuous bedside measurement of CBF and metabolism are available, targeting treatment will require an imprecise balancing of several data sources including the clinical state, CT pattern and evolution and physiological measurements.