20 To Treat or Not to Treat in the Acute Setting (Withholding) and Withdrawal of Treatment

Magnus Olivecrona

Recommendations

Level I

There are no data supporting an individual prognosis at this level.

Level II

There are no data supporting an individual prognosis at this level.

There is prognostic value in age, GCS, GCS motor score, pupillary reaction, hypotension, hypoxia, CT findings, blood chemistry, ethnic origin, and social background.

Level III

There are some data supporting individual prognosis using prognostic models and calculators at this level.

There seems to be some prognostic value in ICP, CPP and PR_x.

There is insufficient evidence for the prognostic value of biomarkers.

There is insufficient evidence to base treatment decisions solely on prognostic calculators and instruments.

Tips, Tricks and Pitfalls

- Be aware that the presentation of poor prognostic factors such as bilateral dilated and fixed pupils does not necessarily mean that the patient will not survive or even have a favourable outcome.
- Be aware of not letting poor prognostic factors become self-fulfilling prophecies.
- There is, at present, no prognostic instrument or tool which allows for prognostication in an individual case, and thus no sole instrument or tool can be used to make treatment decisions in an individual case.

20.1 Overview

Prognosis is derived from the Greek πρόγνωση which means literally "fore-knowing" and "foreseeing".

M. Olivecrona (✉)
Department of Medical Sciences, Faculty of Medicine, Örebro University, Örebro, Sweden

Section for Neurosurgery, Department of Anaesthesia and Intensive Care, University Hospital, Örebro, Sweden

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The prognosis of a condition can be used to discuss the seriousness or likely outcome. It can as such be used as an aid in the information process to the patient and/or her/his relatives. It also gives information to the treating physician about what she/he could expect.

The accuracy of prognosis on group or population level can be very precise. At the individual level, the prognosis is most often considerably less accurate.

There are several factors that prognosticate poor outcome in severe traumatic brain injury. Among these are age, GCS, pupillary dilatation with loss of light reflex, hypoxia, hypotension, intradural mass lesions on the CT scan and presence of subarachnoidal or intraventricular blood on CT scan.

The ultimate use of the prognostication would be that the prognosis was so precise, on an individual level, that it allowed for treatment decisions and thus to individualisation of the treatment and care.

The treating physician has to be aware of the limitations of the prognosis and thus show caution in using the estimated prognosis for making treatment decisions for the individual patient.

There is a risk that a single negative prognostic factor, e.g. bilaterally dilated and fixed pupils, which is, on the group level, a strong negative prognostic factor, will be used as foundation for a treatment decision in an individual patient and thus becomes a self-fulfilling prognostic factor.

20.2 Background

Prognosis of the outcome in head trauma has always interested man. In the ancient literature, references to the prognosis of head trauma are found, e.g. in the Edgar Smith papyrus (n.d.) and in the writings of Hippocrates (1999).

Today, the prognosis of outcome of severe traumatic brain injury is mostly defined in relation to the outcome, measured as GOS or GOSE (Jennett and Bond 1975; Wilson et al. 1998). This can be in relation to every single level of the scales or to different dichotomisations, such as dead/alive or favourable/unfavourable. More recent attempts to prognosticate in relation to more refined outcomes such as quality of life have been attempted (Haller 2017; Norup et al. 2017).

The influence of different prognostic factors on the outcome can be analysed using statistical methods. The influence of a single factor on outcome can be analysed using univariate analysis. This result is of limited value. To adjust for confounders, and/or the influence of other prognostic factors, more advanced statistical methods have to be used, e.g. logistic regression or multivariate analysis. Further statistical modelling can result in prognostic models, which even can have the intension of prognosis at individual level.

Factors analysed for prognostic value can be of different kinds: patient characteristics (e.g. age, sex), admission data (e.g. GCS, blood pressure), or data from the clinical course (e.g. ICP, CPP, seizures). These factors are then analysed against different outcome measures such as GOS, GOSE, or quality of life.

Several attempts have been made to create complex prognostic models using several of the prognostic factors. An interesting observation is that in most of these attempts to create a prognostic model for severe traumatic brain injury, the treatment protocols used are not taken into account.

20.3 Prognostic Factors

20.3.1 Patient Characteristics

Sex: In severe traumatic brain injury, the majority of the patients are men. There is no difference between the sexes in regard to prognosis (Ellenberg et al. 1996; Husson et al. 2010; MRC CRASH Trial Collaborators et al. 2008; Butcher et al. 2007).

Age: Increasing age is a strong predictor for poorer outcome (MRC CRASH Trial Collaborators et al. 2008; Combes et al. 1996; Hukkelhoven et al. 2003; Mushkudiani et al. 2007). Some studies show a breaking point around 30–40 years (Hukkelhoven et al. 2003; Mushkudiani et al. 2007). The most head injury

trials have an upper age limit of 60–70 years; so not so much is known of the prognosis in the elderly (Ostermann et al. 2018; Patel et al. 2010; Wan et al. 2017).

The relation between age and outcome in the paediatric population is not very well studied.

Ethnic origin: There are some studies that indicate that the prognosis in black patients is found to be poorer as compared with Caucasians (Mushkudiani et al. 2007; Perrin et al. 2014; Shafi et al. 2007; Sorani et al. 2009).

Minority status and poorer socio-economic status: There are some publications indicating poorer outcome after moderate and severe traumatic brain injury in people of minority status or in poorer socio-economic status (Arango-Lasprilla et al. 2007a, b).

20.3.2 Injury Severity, Clinical Characteristics

Glasgow Coma Score, Glasgow Motor Score: Both are strong predictors for outcome irrespective of time point for assessment (Husson et al. 2010; MRC CRASH Trial Collaborators et al. 2008; Marmarou et al. 2007a). The assessment of GCS is time dependent in the course of severe traumatic brain injury (Arbabi et al. 2004; Stocchetti et al. 2004). The time point has to be taken into consideration, if the assessment is done in the site of trauma, in the emergency room, after stabilisation, or even after intubation.

In unconscious patients, the motor score has been claimed to be more reliable than the total GCS score (Healey et al. 2003).

The modern care of severe traumatic brain injury includes early intubation and sedation, which has to be taken into consideration (Stocchetti et al. 2004; Balestreri et al. 2005).

We have to bear in mind that a GCS of 3 is an exclusion criterion in many studies; however, papers reporting good outcome (GOS 4–5) in patients with an initial GCS of 3 have been published (Chamoun et al. 2009; Mauritz et al. 2009; Olivecrona et al. 2009a).

Pupillary reaction: The absence of pupillary reaction in one or both eyes is a strong, negative prognostic factor (MRC CRASH Trial Collaborators et al. 2008; Marmarou et al. 2007a). This factor is claimed to be less sensitive for changes over time. In many studies of severe traumatic brain injury, dilated fixed pupil or pupils are an exclusion criterion. There are papers that report good outcome (GOS 4–5) in patients with dilated and fixed pupils (Mauritz et al. 2009; Olivecrona et al. 2009a; Clusmann et al. 2001).

Also loss of pupillary reaction unilaterally is a bad prognostic sign, though not as bad as the loss of pupillary reactivity bilaterally. For poorer outcome, an odds ratio of around 7 for bilateral loss of pupil reactivity has been reported, as compared with an odds ratio of 3 for unilateral loss of pupil reactivity (Marmarou et al. 2007a).

Hypotension: Hypotension, defined as a systolic blood pressure <90 mmHg, is a strong prognostic factor (Butcher et al. 2007; Chesnut et al. 1993a; Miller et al. 1978; Murray et al. 2007; Walia and Sutcliffe 2002). A bell-shaped curve for the impact of blood pressure on outcome has been reported. This curve shows a better prognosis for systolic blood pressures between 120 and 150 mmHg, corresponding to mean arterial blood pressure of 85–100 mmHg (Butcher et al. 2007).

Hypoxia: Hypoxia is a factor for poor outcome (Chesnut et al. 1993a; Miller et al. 1978; Hukkelhoven et al. 2005; McHugh et al. 2007). The definition of hypoxia varies between studies ($S_aO_2 < 90/92\%$ or $P_aO_2 < 8$ kPa).

Abbreviated Injury Scale (AIS), Injury Severity Score (ISSS): These scores are commonly used to describe extracranial injury (Rating the severity of tissue damage 1971; Baker et al. 1974). Whether extracranial injuries affect the prognosis or not has been discussed, and findings in both directions have been reported. It seems that the extent of the extracranial injury has a larger influence in persons with milder brain injury than in persons with severe brain injury. It also seems that the extent of extracranial injury mostly affects the early mortality (van Leeuwen et al. 2012).

20.3.3 Laboratory Parameters

Initial blood glucose: A high blood glucose level correlates positively with poor outcome (Helmy et al. 2010; Van Beek et al. 2007).

Initial sodium levels: Low and high sodium levels are associated with poor outcome (Van Beek et al. 2007).

Haemoglobin: Low haemoglobin is a factor in poor prognosis (Helmy et al. 2010; Van Beek et al. 2007).

Biomarkers: Biomarkers such as S-100B, neuron-specific enolase, and ApoE (ε) have attracted much attention for their possible prognostic value. The findings have been confounding. Some authors find prognostic value in the biomarkers (Nylen et al. 2008; Rainey et al. 2009; Rothoerl et al. 2000; Teasdale et al. 1997; Vos et al. 2010) and some authors do not (Alexander et al. 2007; Olivecrona et al. 2009b; Teasdale et al. 2005).

No biomarker has yet been proven to have a strong predictive value.

20.3.4 Structural Imaging

Computerised tomography: In 1991, Marshall and collaborators introduced a system to classify CT scans. This system was initially designed as a descriptive method (Marshall et al. 1991). The Marshall classification, which focuses on mass lesions, has been correlated to prognosis (Servadei et al. 2000). The importance of the CT scan features for the prognosis was well established in the treatment guidelines published in 2000 (The Brain Trauma Foundation 2000). A combination of different CT features, such as shift of the midline structures, the presence of subarachnoid blood and epidural haematoma, or compression of basal cisterns, increases the prognostic value (Maas et al. 2005, 2007). The presence of subarachnoid blood seems to be one of the strongest predictors of poor outcome (Maas et al. 2005). The Rotterdam classification of the CT scan introduced by Maas and collaborators in 2005 seems to have a stronger predictive value than the Marshall classification (Maas et al. 2005). It also allows for the comparison of the CT scans over time.

Magnetic resonance tomography: MR imaging might have an important role in prognostication after severe head injury. The method is complicated to use in an intensive care setting. In almost all of the studies reporting on MR findings, the investigation has been done at 1 week or later after trauma. Thus, the findings will have little consequence on the early prognostication. The timing of the MR investigation seems to have an influence on the use of the results for prognostication (Moen et al. 2012; Skandsen et al. 2011). On the other hand, it can be a useful tool in understanding the process of the disease.

20.3.5 Clinical Course

Intracranial pressure: Intuitively, one would assume that ICP should be a strong prognostic factor. Some treatment concepts are focused on reducing the ICP (ICP targeted therapy). Most authors report correlations between, e.g. the highest observed ICP and outcome and the mean ICP over at certain time or the "delivered" ICP over time (Farahvar et al. 2011; Vik et al. 2008). The majority of authors do present a prognostic value of ICP (Balestreri et al. 2005; Farahvar et al. 2011; Vik et al. 2008; Marmarou et al. 1991). Strictly, the prognostic value of ICP is difficult to interpret.

Cerebral perfusion pressure: Intuitively, the CPP should be a prognostic factor. The same applies for the CPP as for the ICP; there have been many different ways trying to establish a prognostic correlation. Authors have reported the prognostic value of CPP (Clifton et al. 2002; Juul et al. 2000; Kirkness et al. 2005), and others have reported of the non-prognostic value of the CPP (Balestreri et al. 2006). Strictly the prognostic value of the CPP is difficult to interpret.

Periods of hypotension and hypoxia: There are reports stating that the number and duration of episodes with hypotension and/or hypoxia during the course of treatment correlates negatively to

the outcome (Chesnut et al. 1993a, b; Sarrafzadeh et al. 2001).

Autoregulation, Pressure reactivity—PR index and PR_x: The PR, which is the regression coefficient of several MAP/ICP points, can be regarded as a surrogate measure for the autoregulative state of the brain, with a negative to zero value of the PR regarded as indicator of intact autoregulation. A disturbed autoregulation has been reported to correlate with or even predict poor outcome (Balestreri et al. 2005; Adams et al. 2017; Hiler et al. 2006; Howells et al. 2005; Sorrentino et al. 2012; Zweifel et al. 2008).

20.4 Prognostic Models: To Make a Prognosis

During the last decade, several attempts to construct a prognosis model based on different prognostic factors have been done. One has used pooled data from large series of patients, e.g. from the prospective trials. These data have then been analysed using advanced statistics to produce models of prognostication. One of the goals has been to try to find a model allowing for individualised prognostication.

Some of these attempts have resulted in prognostic formulas or calculators of which some are available on the Internet (see Table 20.1).

Several of these prognostic models have been validated using external data. These validations have found a fairly good reliability (Castano-Leon et al. 2016; Han et al. 2014; Majdan et al. 2014; Olivecrona and Koskinen 2012; Olivecrona and Olivecrona 2013). On attempts to validate these prognostic tools, several authors found a tendency to an overestimation of the risk for poorer outcomes. None of the instruments are good enough to allow for prognostication and thus not allowing for treatment decisions in an individual case. The user of these prognostic tools has to be aware of the limitations of the prognostication.

Table 20.1 Prognostic calculators available on-line

Name	Factors used	Link	Predicts for
IMPACT (Marmarou et al. 2007b)	Clinical data CT findings Laboratory data	http://www.tbi-impact.org/?p=impact/calc	Mortality and unfavourable outcome at 6 months
CRASH (MRC CRASH Trial Collaborators et al. 2008)	Clinical data CT findings	http://www.crash.lshtm.ac.uk/Risk%20calculator/index.html	Mortality at 14 days Unfavourable outcome at 6 months
Nijmegen (Jacobs et al. 2013)	Clinical data CT findings	http://www.tbi-prognosis.com	Mortality at 6 months Unfavourable outcome at 6 months
Helsinki score (Raj et al. 2014)	Clinical data CT findings	http://links.lww.com/NEU/A676	Mortality at 6 months Unfavourable outcome at 6 months
Stockholm score (Nelson et al. 2010)	CT findings Clinical data	Probability score for unfavourable outcome: $1/1 + e^{(3,5\text{-}1,1*\text{tally})}$ Tally = midline-shift (mm)/10 + SAH/IVH-score/2–1 (if EDH) + 1 if DAI + 1(if dual-sided SDH) + 1	Best outcome at 1 year
Stockholm rule of thumb (Nelson et al. 2010)		Probability for unfavourable outcome: Age—3 ∗GCS + mid-line shift (mm) + 10 rule 10 rule = +10 if non-responsive pupils; +10 if SAH/IVH; +10 if DAI; −10 if EDH	Best outcome at 1 year

20.5 To Treat or Not to Treat: Does the Knowledge About Prognosis Help?

When the unconscious trauma victim, i.e. the person with a severe head injury, arrives in the A&E, the receiving physician or surgeon is put to a challenge. She or he has relatively limited information to make difficult decisions, the basic question being to initiate treatment or not.

First of the questions is if diagnostic procedures should be initiated or if the patient e.g. has fixed and dilated pupils upon arrival, the decision to just say that the prognosis is so bad that there is no indication for any kind of diagnostic measures. As the author has tried to outline above, there are so many factors to take into consideration in this decision.

Irrespective of later decisions, one should even in this acute situation try to gather as much information as possible.

To manage this would, in the opinion of the author, be to (if so needed) secure the airway and progress to doing a CT scan, preferable a "trauma CT" including not only the head but also the main part of the body. In this time, there is an opportunity to gather more information about the history of the patient, the circumstances surrounding the accident, and primary clinical and neurological status. This together with the information attained from the CT scan gives valuable information for the decision-making process.

Even though several markers for poor prognosis might be present, we also know that the exactness of the prognosis is not very good at the individual level.

Not to initiate treatment in a young, otherwise healthy person, with an isolated blunt severe head injury, even if the person presents with bilateral, dilated fixed pupils, is a doubtful decision. On the other hand, not to initiate treatment in a person 85 years of age, with bilateral fixed and dilated pupils, would most probably be wise.

The clinical outcome learns, in this author's opinion, that a primary aggressive initiation of treatment is preferable. A good help in early treatment decisions is the use of aggressive ICP monitoring, as it at least to some extent gives information about the risk of cerebral hypoperfusion/ischaemia.

If one starts with an aggressive treatment approach, one also has to be open for continuous re-evaluation of this treatment decision. It is in this process of a continuing re-evaluation of treatment that the knowledge about certain factors' influence on prognosis comes to use. This in a synthesis with clinical experience, local experience, and knowledge about the attitudes of the stricken and its relatives, will build a ground on which the treating physician or surgeon can make decisions about the treatment ambitions, level of treatment, or even withdrawal of treatment.

20.6 Specific Paediatric Concerns

There are relatively few studies of severe traumatic brain injury in the paediatric population. Generally, one can assume the severely injured child has a better prognosis than the adult with a corresponding injury. This might be due to several factors, such as greater plasticity of the young brain, a general better healing capacity, and fewer concomitant diseases.

One recent publication indicates that PR_x has a prognostic value for children (Hockel et al. 2017).

Generally, the recommendation must be to treat a child with severe traumatic brain injury aggressively.

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