CHAPTER 17

Ethical implications of time frames in a randomized controlled trial in acute severe traumatic brain injury

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Abstract: Objectives: To analyze factors determining the time between injury and study drug administration (SDA) in a randomized controlled trial (RCT) of acute severe traumatic brain injury (TBI) and to discuss the ethical implications. Methods: Time frames prior to SDA, differentiated per country, were analyzed in a recently conducted RCT in severe TBI. Per protocol, the time window for SDA was 6 h after injury. We selected patients for whom written proxy consent (PC) was obtained prior to SDA (n = 631). Results: The time between injury and admission to the neurotrauma center (NTC) varied per country from 1.16 to 2.35 h, but CT scan was obtained on average within 1 h of admission. The median time between injury and CT scan was within 3 h in all but one country. The broadest time window was observed between CT scan and obtaining required PC (1.71–2.74 h). The median time between injury and PC varied between countries from 3.75 to 5.00 h. After consent had been obtained, almost all patients subsequently received study drug within 1 h. In 85.3% of all cases time between injury and SDA exceeded 4 h, in 60% 5 h. Conclusions: The requirement of written PC causes a significant delay in SDA in TBI. With deferred consent, the first dose of an investigational drug could potentially be administered directly after completion of the admission CT scan, which reduce the time to SDA by 50%. We argue that randomization under deferred consent is ethically defendable for emergency research in severe TBI. Recommendations for patient protection are proposed.

Keywords: traumatic brain injury; informed consent; emergency trial; deferred consent

Introduction

Severe traumatic brain injury (TBI) remains a major cause of death and disability afflicting mostly young adult males and elderly people, and results in high economic costs to society (McGarry et al. 2002). The fatality rate for severe TBI is about 30% and a significant disability persists in a further 35–40%. These data signify an ethical imperative to develop and test neuroprotective agents and other new therapeutic strategies. Various neuroprotective agents, mainly targeting specific pathophysiologic mechanisms, have been tested in TBI, but convincing benefit has not been shown (Maas et al., 1999). Randomized controlled trials (RCTs) in emergency and intensive care medicine pose complex ethical and methodological

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challenges (Maas et al., 2004; Kompanje et al., 2005).

Specific ethical issues pertaining to clinical testing of neuroprotective agents in TBI include the emergency nature of the research, the incapacity of the patients to informed consent before inclusion, short therapeutic time windows, and a risk–benefit ratio based on concept that in relation to the severity of the trauma, significant adverse side effects may be acceptable for treatments with proven benefit. The relevance of these issues and implications for trial design are, however, not fully recognized in- and outside the expert field. Legislation in countries in the European Union is being amended to comply with the European Union Directive 2001/20/EC (European Union, 2001). In this new European legislation, emergency research under deferred or waiver of consent is not permitted. This will impede or even obviate emergency research phase III trials in TBI in the European countries (Kompanje and Maas, 2004; Silverman et al., 2004; Liddell et al., 2006a, b).

We aimed to analyze the implications of critical time frames (time between injury and admission to a neurotrauma center (NTC), between admission and the first cranial CT scan, between CT scan and proxy consent (PC), and between PC and study drug administration (SDA)) in a recently completed RCT in TBI.

Materials and methods

We analyzed critical time frames in a multi-center placebo-controlled phase III trial, investigating the efficacy and safety of a single dose of dexanabinol in severe TBI. This RCT was conducted from January 2001 to March 2004 in Europe, Israel, Australia, and the United States. Dexanabinol is a synthetic cannabinoid analogue with strong neuroprotective potential and devoid of psychoactive activity. The protocol stipulated SDA within 6 h after injury. The study recruited 861 patients with severe TBI. No beneficial effect of dexanabinol was found. Full details and results of the study have been published (Maas et al., 2006).

In total, 7164 patients were screened for participation in the trial. Enrollment criteria were not met in 6303 patients. Of these, the sole reason for exclusion was the time window in 671 patients and in a further 944 patients inability to give study medication within 6 h was one of the reasons for exclusion (Fig. 1).

![Time window as main reason for exclusion](image-url)

Fig. 1. Reasons for exclusion (n = 6303).
In view of the severity of the brain injury, informed consent could not be obtained from the patients themselves. PC was accepted in all countries. Deferred consent was allowed in Australia, Austria, Finland, and in some centers in France and Germany. Consent by an independent physician was allowed in Israel, Italy, Spain, and the United Kingdom. In all cases of deferred consent, subsequent written assent by patient or proxy was obtained.

For the analysis of time frames we selected patients enrolled in Europe and Israel, in whom PC was obtained before SDA \( (n = 631) \). We excluded patients from the United States for reason of incomplete screening logs due to HIPAA regulations (Maas et al., 2005; Kompanje and Maas, 2006), and patients from Australia seeing the different infrastructure of this country in comparison to European countries.

### Results

The median age of our study population was 32 years (IQR 23–44); 520 (82.4%) were male, 111 (17.6%) female. The time between injury and admission to the NTC varied between countries from 1.16 to 2.35 h (Table 1, Fig. 2). A total of 501

<table>
<thead>
<tr>
<th>Country (N)</th>
<th>Hours between injury and admission NTC median (IQR)</th>
<th>Hours between injury and CT scan median (IQR)</th>
<th>Hours between injury and obtained consent median (IQR)</th>
<th>Hours between injury and SDA median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium (23)</td>
<td>0.93 (0.65–1.27)</td>
<td>1.80 (1.28–2.27)</td>
<td>3.75 (2.75–4.75)</td>
<td>4.60 (3.98–5.42)</td>
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<tr>
<td>Netherlands (73)</td>
<td>1.00 (0.75–1.33)</td>
<td>1.65 (1.32–2.00)</td>
<td>4.53 (3.95–5.05)</td>
<td>5.53 (5.07–5.75)</td>
</tr>
<tr>
<td>Israel (116)</td>
<td>0.93 (0.72–1.40)</td>
<td>1.91 (1.58–2.47)</td>
<td>4.01 (3.20–4.83)</td>
<td>4.67 (4.00–5.33)</td>
</tr>
<tr>
<td>Spain (75)</td>
<td>1.33 (0.97–1.67)</td>
<td>2.07 (1.65–2.53)</td>
<td>4.17 (3.33–5.00)</td>
<td>5.17 (4.30–5.58)</td>
</tr>
<tr>
<td>Germany (109)</td>
<td>1.20 (0.88–2.00)</td>
<td>1.65 (1.30–2.13)</td>
<td>4.08 (3.42–4.98)</td>
<td>5.25 (4.25–5.67)</td>
</tr>
<tr>
<td>Italy (146)</td>
<td>1.25 (0.83–2.60)</td>
<td>1.77 (1.40–2.35)</td>
<td>4.92 (4.08–5.28)</td>
<td>5.50 (4.98–5.75)</td>
</tr>
<tr>
<td>France (34)</td>
<td>2.17 (1.42–3.00)</td>
<td>3.08 (1.97–3.53)</td>
<td>5.00 (4.50–5.38)</td>
<td>5.75 (5.17–5.83)</td>
</tr>
<tr>
<td>Other countries(^a) (55)</td>
<td>1.47 (1.00–2.67)</td>
<td>1.82 (1.33–2.50)</td>
<td>4.00 (3.08–4.75)</td>
<td>5.25 (4.33–5.75)</td>
</tr>
</tbody>
</table>

\(^a\)Countries with small patient populations (United Kingdom, Denmark, Austria, Poland, and Turkey) were combined.

Fig. 2. Time between injury and admission neurotrauma center, time between admission and first CT scan, time between first CT scan and informed consent for inclusion in trial and time between consent and start study drug admission.
(79.4%) patients were directly admitted to the NTC, and 130 (20.6%) concerned secondary referrals. In 71 secondarily referred patients the CT scan was made before admission to the NTC. The time between admission and the first diagnostic CT scan was within 1 h in all patients. With the exception of France, in all countries the median time between injury and CT scan was within 3 h (Table 1). The broadest time window was found between the admission CT scan and obtaining the required PC (between 1.71 and 2.74 h). The median time between injury and obtained PC varied between 3.75 and 5.00 h (IQR 2.75–5.38 h) (Table 1). After consent had been given, almost all patients subsequently received the study drug within 1 h (Table 1, Fig. 2). In 85.3% of all cases the time between injury and SDA exceeded 4 h, in 60% of the cases it even exceeded 5 h (Fig. 3). In total, 139 patients were randomized with deferred consent. The median time between injury and SDA in this group was 4.75 h (IQR 3.90–5.67). These 139 patients are not included in our analysis.

Discussion

Specific ethical issues pertaining to clinical evaluation of neuroprotective agents in TBI include the emergency nature of the research, short therapeutic windows, the incapacity of the patients to informed consent before inclusion, and a risk–benefit ratio based on the concept that in relation to the severity of the trauma, significant adverse side effects may be acceptable for treatments with proven benefit (Kompanje et al., 2005).

The emergency nature of research and short therapeutic time windows in TBI

Severe TBI is an emergent and life-threatening condition and existing therapy is unsatisfactory given the high morbidity and mortality. Neurological damage does not only occur at the moment of impact, but can evolve over the following hours and days. Deleterious effects of this progressive damage are determined at clinical and biochemical levels. This has led to the development of new pharmaceuticals with promising potential to limit secondary damage and to improve outcome. One of these new pharmaceuticals was dexanabinol, but efficacy in the treatment of severe TBI was not demonstrated (Maas et al., 2006). Recruitment in this study was relatively slow and the majority of patients enrolled toward the end of the 6 h time window stipulated in the protocol. We hypothesized that the relatively slow recruitment and lack of demonstrable efficacy in the clinical situation may have been influenced by informed consent procedures and resulting delays in SDA. Early intervention would appear crucial to the effect of neuroprotective agents. Experimental data have consistently shown better protection the sooner an agent is administered after TBI (Hoff, 1986). For dexanabinol, experimental studies have shown beneficial effects with administration within 3 h after injury, demonstrating protection against breakdown of the blood-brain barrier, reduction of edema formation, and improved outcome (Shohami, 1995). No significant reduction of cerebral edema was noted if the drug was administered between 4 and 6 h after injury, but some improvement in neurological symptoms was found. Based on these findings, it may be concluded that in the experimental model the pathophysiologic time window can be determined at 3 h. Whether this experimental time window may be extrapolated to the clinical situation in patients with TBI remains
uncertain. Prespecified subgroup (patients who received the SD within 4 h and patients who received the SD after 4 h) analysis showed no significant differential treatment effect (Maas et al., 2006). Nonetheless, it may be concluded in general that chances of efficacy are greater if treatment is provided earlier. We found that in almost all of the studied cases the time between injury and completion of the primary diagnostic CT scan remained within 3 h post injury, which corresponds to the therapeutic time window in the animal model. In 60% of the cases, however, the time between injury and SDA was more than 5 h, and in 85.3% of all cases more than 4 h (Fig. 3).

We have shown that the main determinant of the time to SDA is formed by the time required to obtain informed (proxy) consent, and these results indicate that delays in SDA could be reduced by 50% with the adoption of deferred consent or waiver of consent. We could, however, not demonstrate shorter inclusion times in the cohort of patients randomized with deferred consent. The reason for the delay in this cohort was that most investigators waited for PC before randomization, and only used deferred consent when at the end of the inclusion boundary. These observations favor adopting deferred consent procedures in trials in acute TBI as primary approach, rather than as “ultimo refugium”, only to be undertaken if PC cannot be obtained. Other studies have demonstrated advantages in using the deferred consent and waiver of consent in emergency research. In the National Acute Brain Injury Study: Hypothermia (NABIS-H) the adoption of waiver of consent resulted in higher enrollment and reduced the time between injury and treatment by approximately 45 min (Clifton et al., 2002). In this study, relatives of only 11 out of 113 patients arrived within 6 h after the injury. In a septic shock trial the investigators could not contact the proxies within the inclusion time in 74% of the cases, and these were included under waiver of consent (Annane et al., 2004). In the CRASH trial, mean time to randomization was significantly longer in those hospitals where consent was required compared with those it was not (4.4 h [SE = 0.21] versus 3.2 h [SE = 0.16]), the difference in the mean time to randomization was 1.2 h [95% CI 0.7–1.8 h] (CRASH trial management group, 2004). The observation in the cohort of patients enrolled in the dexanabinol trial with deferred or waiver of consent, that (proxy) assent was obtained later in all cases supports the concept of accepting deferred or waiver of consent for emergency research in TBI trials.

The acute incapacity of the patients and informed consent

All patients with severe TBI are unconscious, and consequently informed consent can never be obtained from the patients themselves. As substitute for informed consent, a legal representative must give consent for inclusion in research, or in the absence thereof, by proxies; alternatively consent may be deferred or waived. We have argued that deferred consent is preferable. However, the new European Union Directive (2001/20/EC) (European Union, 2001; Liddell et al., 2006a, b) stipulates a requirement for informed (proxy) consent. This is motivated by respect for the autonomy of patients, and to ensure that that patient’s wishes are guaranteed as far as possible. The requirement for PC assumes that relatives are available in emergency situations, and that these relatives can be fully informed and given sufficient time to make a balanced, ethically valid decision in a relatively short time period under emotional distress. Even when proxies are available, many are not aware of the patient’s wishes (Luce, 2003). Surrogate decision makers for critical care research resulted in false-positive consent rates of 16–20.3% (Coppolino and Ackerson, 2001). The emotional nature of an emergency situation limits the reliability of PC for clinical research (Mason and Allmark, 2000; Coppolino and Ackerson, 2001; Hsieh et al., 2001). Under emergency circumstances, PC does not seem to secure proper patient/subject protection. In our experience, the validity of informed consent and PC given in an emergency situation is at least troubling. When consent for clinical research is sought during an emergency situation, comprehension is generally less than optimal (Cuttini, 2000; Sugarman, 2000; Williams et al., 2003). A small minority realizes that pharmacological
trials are designed to assess not only efficacy but safety as well (Harth and Thong, 1995). Are patients willing to be represented by their close relatives? Roupie et al. (2000) found that only 40.6% of 1089 patients wanted their spouse/partner to be their surrogate, 28% wanted to be represented by the physician in charge of their care.

One study searching for public views on emergency exception to informed consent found that most of 530 people (88%) believed that research subjects should be informed prior to being enrolled, while 49% believed enrolling patients without prior consent would be acceptable in an emergency situation and 70% (369) would not object to be entered into such a study without providing prospective informed consent (McClure et al., 2003). In another study 11 of 12 stroke patients stated that, if the patient or family was not able to consent, the treating physician should make the decision for inclusion in an emergency trial (Blixen and Agich, 2005).

Furthermore, the requirement for all patients to give written informed consent before enrollment can result in major selection biases, such that enrolled patients may not be representative of the typical patient (Tu et al., 2004).

Although respect for a patient’s autonomy is a guiding principle in human rights, we doubt very much whether this can be guaranteed by mandatory PC in acute TBI research. A balance should be sought between optimal patient protection and research to advance the standards of clinical care in emergency situations to the benefit of society.

Risk–benefit ratio and patient protection

In our opinion the balance between risk and benefit should be the guiding principle in emergency research in severe TBI. This also applies to the nature and the type of consent procedures. The ethical principle of respect for the autonomy of the patient underpinning the informed consent procedures is not valid for acutely incapacitated patients as TBI victims (Kompanje et al., 2005). Significant concerns have been raised on the validity and ethics of PC in acute emergency situations, and the required written consent causes a significant delay in treatment initiation, as we have shown by our analysis. The possible therapeutic benefit, with short therapeutic time windows in experimental models, forms the moral justification for randomizing patients under deferred consent or waiver of consent within a sufficient period of time. The risks should however be acceptable in relation to the severity of the disease or injury.

For an effective agent in life-threatening conditions adverse effects may be expected and accepted in some patients. Careful monitoring and follow-up of such adverse events is mandatory.

For trials under deferred consent or waiver of consent in acute emergency situations we propose to institute an independent safety committee, under the auspices of regulatory authorities. Such an independent safety committee, without (financial) ties to industry or investigators, offers the best safeguard for patient protection. The obligation to such a committee is based on the experience of a dramatically harmful outcome in some trials under waiver of consent in other fields of medicine (Freeman, 2001; Lewis et al., 2001).

Clinical research in emergency situations without prospective informed or PC is ethically challenging. Severe TBI is without doubt an emergent and life-threatening condition and existing therapy is unsatisfactory. This should qualify severe TBI as emergency exception to informed consent or deferred consent for randomized clinical controlled trials involving pharmacological agents with promising therapeutic benefit facing short therapeutic time windows. Randomized placebo-controlled investigations are necessary to determine the safety and efficacy of new developed agents under these circumstances. The requirement for prior written PC causes significant delays in SDA. With deferred consent or waiver of consent the first dose of the experimental drug can be administered directly after completion of the first diagnostic CT scan, which is very close to the experimental therapeutic time window. Randomized controlled phase III trials investigating the safety and efficacy of agents with promising benefit, conducted in acute emergency situations with short therapeutic time windows, should allow randomization under deferred consent or waiver of consent. This is ethically defendable, of course
with proper safeguard from an independent safety committee. Making progress in knowledge of treatment in acute neurological and other intensive care conditions is only possible if national regulations and legislations allow waiver of consent or deferred consent for clinical trials (Lemaire, 2005). As two of us have said before: ‘treat first, ask later’ is ethically defensible in emergency and intensive care medicine research (Kompanje and Maas, 2004).

References


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