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Ethical considerations on consent procedures for emergency research in severe and moderate traumatic brain injury

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Summary

Therapeutic trials in TBI are subject to principles of Good Clinical Practice (GCP), to national legislation, and to international and European ethical concepts and regulations [e.g. 13]. The guiding principles underlying these investigations of treatment are respect for autonomy of research subjects, protection against discomfort, risk, harm and exploitation and the prospect of some benefit. Patients with significant TBI are mentally incapacitated, thus prohibiting obtaining consent directly from the subject. Various approaches to consent procedures are used as surrogate to subject consent: proxy consent, consent by an independent physician and waiver of consent. These approaches are reviewed. A questionnaire soliciting opinions was mailed to 148 EBIC (European Brain Injury Consortium) associated neuro-trauma centers in 19 European countries. 48% respondents believe that relatives were not able to make a balanced decision, 72% believed that consent procedures are a significant factor causing decrease in enrollment rate and 83% stated that consent procedures delay initiation of study treatment, resulting in possible harm if the agent has shown to be effective. 64% of the respondents considered TBI an emergency situation in which clinical research could be initiated under the emergency exception for consent. In new European legislation, emergency research under waiver of consent is not permitted. Nevertheless, we consider that randomising patients with TBI into carefully evaluated trial protocols without prior consent may be considered ethically justified.

Keywords: Traumatic brain injury; proxy consent; waiver of consent; randomised controlled trails; European Union.

Introduction

Severe Traumatic Brain Injury (TBI) remains a major cause of death and disability primarily afflicting young adult males and elderly people, resulting in high economic costs to society. Road traffic accidents, (domestic) falls and assaults are the main causes of TBI.

Although the overall incidence of hospital admissions for mild TBI has decreased in the developed countries [4, 10, 12, 30] reflecting combined effects of preventive measures and more restrictive admission policies, the number of patients admitted with more severe injuries has remained fairly stable. Fatality rates of 26 to 36% and significant disability in a further 35 to 40% of patients admitted with severe injuries are reported in unselected series [22, 31]. These data signify an ethical imperative to develop and test neuroprotective agents and new therapeutic strategies.

Therapeutic trials are subject to principles of Good Clinical Practice (GCP), to national legislation, and to international and European ethical concepts and regulations [e.g. 13]. The guiding principles underlying these investigations of treatment are respect for autonomy of research subjects, protection against discomfort, risk, harm and exploitation and the prospect of some benefit. This prospect is complicated by the equipoise underpinning the statistical null hypothesis of trials: the hope that an individual patient will benefit, but that this is not more certain than the chance of non benefit.

Specific issues pertaining to clinical trials in TBI include the emergency nature of research, the incapacity of subjects to consent, short therapeutic windows, and a risk/benefit ratio based on the concept that in relation to the seriousness of disease or trauma, significant adverse side effects may be acceptable for treatments with

proven benefit. The importance and potential implications of these issues are not fully recognised outside – and even within – the expert field.

The aim of this article is to explore general principles of trials in TBI in more depth, and to evaluate the opinion of investigators on these issues. This is considered relevant as currently national legislation and procedures in clinical trials are being amended in the countries of the European Union to comply with the European Union Directive 2001/20/EC. In the new European legislation, emergency research under waiver of consent is not permitted. The EU directive is a valuable document and deserves respect, but its strict regulations on prior written proxy consent in the case of acutely unconscious patients impede or even obviate emergency research Phase III trials in TBI in the European Union.

Time windows for emergency research in TBI

TBI is by definition an acute disease. Experimental and clinical studies have shown that pathophysiological cascades are initiated within minutes to hours following injury. Time windows for treatment are therefore considered to be short. Experimental studies have shown the efficacy of many neuroprotective agents, if these were administered before, or within 15 minutes after injury; others showed a window of efficacy of 3 to 6 hours. It is however uncertain whether these experimental time windows can be translated directly to the clinical situation and the general conclusion is that chances of efficacy increase if treatment is provided earlier.

Time windows as applied to randomised controlled trials in TBI have rarely been based on experimental evidence, but were rather determined by organisational and logistical considerations as to the time window within which investigators expected that a considerable number of patients could be enrolled. Most studies used a time window of 8 hours, one a time window of 4 hours and some allowed inclusion up to 12 or even 24 hours after injury. Experience is that treatment initiation is very often delayed to the last hour of the specified time window. The main determinant is informed consent procedures, when consent by a legally acceptable representative is required by local or national regulations. These procedures require first of all that relatives are available, and secondly that they are fully informed and are given sufficient time to make a balanced decision or that other mechanisms are applied if relatives are not available such as a court decision.

Considerable intercenter and intercountry differences in availability of relatives exists, being influenced by distances, local trauma organisation and referral policy. As injuries mostly occur outside the domestic situation, family members are rarely available during the first hours after traumatic injury. Wright *et al.* (2001) [33], studying the next of kin contact and next of kin arrival to hospital in a series of 332 patients with severe and major trauma report that only 28% of patients were accompanied by relatives on arrival. For unaccompanied patients the average time for contacting relatives of conscious patients was 59 minutes, for relatives of unconscious patients 78 minutes. This study demonstrates that, even in centers with short referral times, the availability of relatives for giving proxy consent for emergency research is a limiting factor, especially when time windows are necessarily short. The conflict between the desire for early initiation of treatment with the time required for consent procedures is illustrated by the National Acute Brain Injury Study: Hypothermia (NABIS-H) in which adoption of waiver of consent resulted in a higher enrollment rate and reduced the time to treatment by approximately 45 minutes [8]. Relatives of only 11 patients out of a total of 113 subsequently arrived within 6 hours of the injury. In a recent septic shock trial the investigators could not contact the responsible relative within the inclusion period in 74% of the cases (220/300 patients) and these patients were included under waiver of consent [2]. Further study of the availability of proxies for consent to emergency research in European countries is needed.

Consent procedures

patients with significant TBI are suddenly mentally incapacitated and generally remain so for longer periods of time, thus prohibiting obtaining consent directly from the subject. Various approaches to consent procedures are used as surrogate to subject consent: proxy consent, consent by an independent physician and waiver of consent.

Proxy consent

Most ethical committees and institutional review boards in European countries, as well as in North America, consider consent by legal representatives valid and have pragmatically accepted consent by those who, according to national law are legally acceptable as representatives (e.g. relatives). This is considered a valid surrogate with respect to the protection of the rights of incapacitated patients in acute care research and provides protection

from possible exploitation by investigators. Proxy consent does not have the same moral value as consent by the subject, as autonomy of the patient is lost due to the injury and this can therefore no longer be a guiding principle. The moral basis for proxy consent is restricted to the substituted judgement about the research proposal. The proxy is supposed to act as his/her relative, if competent, would have decided.

But do patients really want to be represented by their relatives? Roupie *et al.* (2000) studied the wishes of 1089 French patients about medical information and surrogate decision making in non-research settings and found that 29% stated that they would not want family members as surrogates if they should become incapacitated. Only 41% (229/561) of the patients living with a spouse or partner wanted them to represent their interests, and 29% reported that they preferred to be represented by the physician in charge of their care rather than by a surrogate family member. Although this study concerned proxy consent for standard treatment, it can be assumed that similar results will apply to research situations.

It is doubtful whether proxies will indeed make similar decisions as patients would. Coppolino & Ackerson (2001) [9] concluded that surrogate decision makers for critical care research resulted in false-positive consent rates in up to 20%. Sulmasy *et al.* (1994) [29] studied the wishes of 50 patients and their proxies for treatment in 3 scenario's of coma and brain damage, and found that agreement between patients and their proxies varied between 57% and 81%, depending on whether previous discussions had taken place on similar situations. It is unlikely that such existential discussions occur frequently in the population of young adult males, prone to TBI, and proxies lack evidence what their relative would have wanted in such situations. Most proxies seem to make decisions in emergency and life threatening situation based on what they hope will happen (survival of their loved one), rather than what is likely to happen (facing possible death or disability); this will bias decision making towards possible therapeutic benefit, however small that chance may be [21].

'Consent' by independent physician

In some European countries the primary approach to consent procedures for emergency research is randomisation by an independent physician who has no involvement in the research and no interest in including patients in the trial, even if proxy consent might be feasible. In other countries, this approach is only adopted if proxy consent is not possible. Consent by an independent physician is not equivalent to informed consent nor to proxy consent, as no attempt is made to respect the autonomy as leading principle, nor can any inference be made concerning the subjects personal opinion. It can therefore only be seen as a justification for non-individual based surrogate decision making in the light of beneficience of the whole trial group in emergency situations. The different perceptives on consent by an independent physician are reflected in conflicting reports: 84% of patients with myocardial infarction felt that the physician could independently decide on inclusion to an intervention, if the patient was too ill to be asked for consent [1]. In the field of neonatology however only 11% of parents believe that the medical staff should be left to decide independently regarding research participation [21].

Waiver of consent

The terms ''deferred or retrospective consent'' and ''waiver of consent'' are sometimes used as a form of consent adopted in situations in which it is impossible to obtain consent from the patient as a potential research subject, from his/her representatives or relatives, and involves randomisation of patients at the discretion of the investigator/physician. After inclusion of the patient into the study, the patient or his/her representatives or relatives should be informed as soon as possible and subsequent informed consent or proxy consent for continuation in the study should be requested. Deferred consent is frequently mentioned as a general emergency exception to informed or proxy consent, and has been used in several randomised controlled trials in TBI in the 1980's and 1990's [8, 20]. The term ''waiver of consent'' is used more often to allow research without prior consent on patients in life threatening situations in an emergency setting. The moral demand to avoid exploitation of subjects who would not be able to give consent by themselves remains pertinent, but at the same time it would be wrong to deprive them and future patients of the opportunity to possibly benefit from the research. Emergency research without prior consent can be accepted on grounds of fairness and justice. The WHO declaration of Helsinki mentions the waiver of consent in an emergency setting, stating: ''if the physician considers it essential not to obtain informed consent, the specific reasons for the proposal should be stated in the experimental protocol for transmission to the

independent committee''. In 1996, the US-FDA released its final rule for waiver of consent in emergency situations and the American Department of Health and Human Services (DHHS) released an update of its regulation relating to this issue. These regulations include the requirement that

a) the patient is in a life threatening situation
b) available therapies are unproven or unsatisfactory
c) it is not feasible to obtain consent because of the patient's condition while therapies must be commenced before surrogates can be reached
d) research can not reasonably be conducted otherwise
e) the risks and benefits of the experimental procedure are considered reasonable in relation to the patient's current condition and to what is known about other available therapies
f) participation in the study yields the prospect of a possible direct and real benefit to the patient.

Basic criteria for waiver of consent in certain emergency research circumstances were revised in April 2001 in the Code of Federal Regulation of the FDA. These revised regulations recognise that in patients with acute life threatening disorders an increased risk of experimental procedures may be acceptable. An Institutional review board should decide if waiver of consent is permitted in a specific trial.

Many perspectives exist on consent procedures and for this reason we conducted a survey among investigators active in the field of TBI. An initiative was endorsed by the Executive Committee of the European Brain Injury Consortium (EBIC).

The EBIC survey on consent procedures in TBI

A questionnaire soliciting opinions rather than current practice (Table 1) was mailed to 148 EBIC associated neuro-trauma centers in 19 European countries. The survey included questions on the validity and moral justification of the proxy consent in emergency situations, and whether proxy consent was seen as a significant factor limiting enrollment or causing delays in initiation of study treatment. In response to the changing European legislation and the resulting differences between accepted procedures in the US and Europe we specifically asked the respondents if they believed that TBI is an emergency situation in which clinical research can be initiated under the emergency exception of consent.

The response rate was 53% (n = 79). 99% of respondents considered clinical trials necessary to improve treatment results in TBI. This is not surprising as all respondents are working in the field of TBI care, facing a high morbidity and mortality in patient treatment with modern standard therapy. Consent by a legally acceptable representative was considered mandatory in 66% of centers prior to enrollment. 48% of 78 respondents however believe that relatives were not able to make a balanced decision under the emotional and stressful emergency conditions. 72% of the respondents further believed that consent procedures are a significant factor causing decrease in enrollment rate and 83% stated that consent procedures delay initiation of study treatment, resulting in possible harm if the agent has been shown to be effective. 64% of the respondents considered TBI an

Table 1. *Results of the EBIC questionnaire on consent procedures in TBI (not all 79 respondents answered all 10 questions)*

	Yes	No	Don't know
Do you believe that controlled clinical trials investigating new therapeutics are essential for improving quality of care in patients with TBI? (n = 79)	99%	0%	1%
Do you think that universal rules, guidelines and regulations guiding human experimentation fully apply to research in patients with TBI? (n = 79)	66%	25%	9%
Do you consider consent by relatives a valid approach in TBI research? (n = 79)	75%	20%	5%
Is it required to obtain consent by relatives in your center before enrolling a TBI patient into a Phase III trial? (n = 79)	66%	29%	5%
Do you consider it ethically justified to approach relatives of a TBI victim within hours after admission for requesting proxy consent? (n = 77)	76%	19%	5%
Do you feel relatives can make a balanced decision in such a case? (n = 78)	48%	44%	8%
Do you consider proxy consent equivalent to consent by a legal representative? (n = 78)	58%	42%	0%
Do you believe that informed consent procedures are a significant factor causing decrease in enrolment rate?	72%	28%	0%
Do you believe that informed consent procedures are a significant factor causing delays in initiation of study treatment? (n = 78)	83%	17%	0%
Do you believe that TBI is an emergency situation in which clinical research can be initiated under the emergency exception for consent? (n = 79)	64%	35%	1%

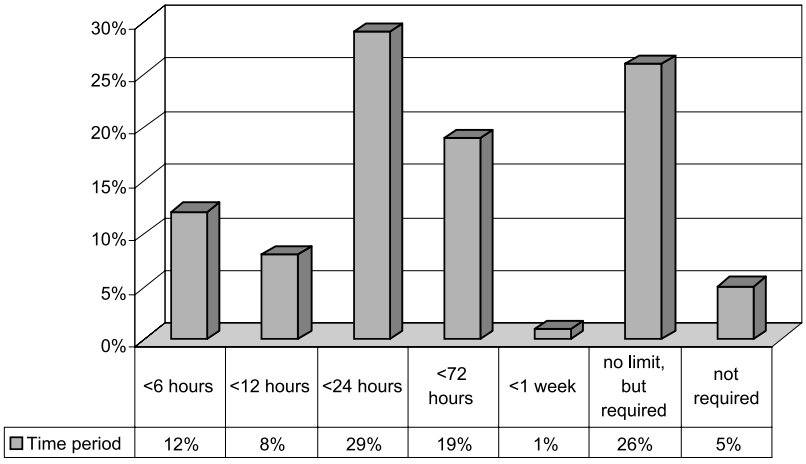

Fig. 1. Within which time period should proxy-consent be obtained or information provided? (n = 77)

emergency situation in which clinical research could be initiated under the emergency exception for consent; 95% of respondents however did feel that proxy consent should be requested later but opinions concerning the most appropriate time for such a request varied (Fig. 1). Full results of the questionnaire are represented in Table 1.

Synthesis and discussion

Ethical considerations in TBI trials are related to the emergency nature of the disease and the acute incapacity of patients, rendering them unable to decide on participation themselves and to provide informed consent. In our analysis we have identified 3 problematic or conflicting aspects relating to specific issues in clinical trials in TBI:

1) The conflict between the desire for early initiation of treatment versus time required for following informed consent procedures.
2) The conflict between the desire for following informed consent procedures and doubts about the validity of proxy consent in emergency situations.
3) Different perspective on applicability of waiver of consent.

Guiding principles for informed consent procedure are respect for the autonomy of patient and optimal protection. Such procedures however take time, decrease enrollment and delay initiation of treatment, according to opinions expressed in the survey and confirmed by the experience in the NABIS-H study. Consent by a legally acceptable representative is currently required in the majority of European centers; we expect this percentage to increase after implementation of national legislation following the directive from the European Union on clinical trials. Too strict implementation of the directive, following the letter rather than the intent, may hinder therapeutic phase III research during the acute phase after TBI. This opinion has been expressed by many others in the field of emergency research in general [18, 24, 27] and in TBI in particular. Patients may consequently be deprived of potentially effective treatments which can be regarded unethical in relation to the high mortality and severe morbidity within this group of patients [2, 11, 16]. The Directive states that additional protection should be provided to incapacitated patients and that written informed consent must be obtained from a legal representative prior to enrollment.

The moral basis for proxy consent is a substituted judgement on what a patient who lacks decision making capacity would have decided. No information is, or probably ever will become available whether individual patients with TBI would have given consent to participation in research if they had been in a position to do so. Some analogy may exist between procedures utilised in patients with severe TBI and in patients with acute traumatic spinal cord injury. Both populations relate to serious emergency situations, and time windows for opportunity of treatment are short, but unlike patients with TBI those with spinal cord injury are not unconscious.

Three randomised controlled trials of the national acute spinal cord injury study showed that out of a total of 1392 patients only 76 (5.45%) refused consent [5–7].

Uncertainty exists whether the substituted judgement would concur with the patient's judgement. Little is known about the quality and validity of proxy consent in emergency settings regarding adult subjects; published results on proxy consent in emergency settings in neonatology and pediatrics give rise to concern. Time

pressures and overwhelming emotions may well decrease the value of proxy consent for emergency in the field of TBI, and our impression is that fear of possibly withholding a prospect of benefit is a strong motivation for proxies to give consent. What is the value of proxy consent when given by a proxy who can not make a balanced decision?

Most probably this outcome reflects a regime of bureaucracy (it is required, we need the signature to enroll the patient), rather than true ethical (by obtaining proxy consent we respect the patients wishes and act in the patients best interests) motives. We feel that the validity of proxy consent obtained in emergency situations should be questioned and subject of further research efforts. The risk exists that proxy consent in such situations constitutes little more than a form of ratification under false pretences of respecting an individual's autonomy.

TBI can be considered an emergency situation in which clinical research can be initiated under the emergency exception for consent. Not using waiver of consent in emergency trials in TBI was the primary cause of decrease in accrual and delay in treatment initiation in the NABIS-H trial [8], consistent with previous experience. In the US the revised regulations of the DHHS permit waiver of consent in such situations. A further consideration is whether and if so, within which time period proxy consent should subsequently be obtained after use of waiver of consent. In our survey most investigators favoured procedures for requesting consent for continuation, and pragmatically suggested a 24 hours window, which would allow for more balanced decision making. We consider it mandatory that following recovery of consciousness subjects are informed of the nature of the study they were enrolled in and that consent for continued participation and use of data is requested. A further safeguard in respect to patient protection is guaranteed by the process of review of all trials by institutional review boards.

In our opinion the balance between risk and benefit should be the guiding principles regarding emergency research in TBI. These principles also apply to the nature and type of informed consent procedures to be followed. The ethical principle of respect for the autonomy of a patient underpinning informed consent procedures is not valid for acutely incapacitated patients such as in TBI. There are significant concerns on the validity of proxy consent in emergency situations, and the required informed consent procedures cause a delay in treatment initiation.

Possible therapeutic benefit can be a moral justification for randomising patients without their consent or the consent by proxies. A trial including patients without prior consent can be ethical if treatment is promising, but unproven, provided that the risks are considered acceptable in relation to the severity of the disease [2, 19]. Unfortunately dramatically harmful outcomes (e.g. significantly more deaths in the treatment group) have occurred in some emergency randomised controlled trials under waiver of consent in other fields of medicine [15]. A pre-requisite for patient protection is careful and independent safety monitoring to limit risks. Current practice is that safety monitoring committees, although independent, are confirmed and sponsored by pharmaceutical companies initiating trials of neuroprotective agents, consequently leading to a potential conflict of interest. For trials conducted under waiver of consent we would prefer the institution of an independent safety committee, under the auspices of regulatory authorities.

Subject to these conditions we consider that randomising patients with TBI into carefully evaluated trial protocols without prior consent may be considered ethically justified. Strict prospective judgement of possible risks in relation to the severity of the disease or condition should be the guiding principle in allowing research under waiver of consent.

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Comments

This is a superb piece of solid, pragmatic bioethics and most timely since we all fear the autocratic squeezing from the E. U. (now presided over by a Portuguese. . .). It is time to rehabilitate the virtues of a well tempered paternalism, which I always found is much more demanding, morally speaking, than the safe adherence to the principle of the supremacy of autonomy. Paternalism carries quite often more beneficence and this is the ultimate goal of good scientific inquiry.

João Lobo Antunes
Lisbon

This thoughtful manuscript by Kompanje *et al.* reviews the problems of attempting to obtain consent for patient enrolment in research studies of emergency treatment for severe brain injury. On the one hand, respect for a patient's autonomy demands that the patient be given the opportunity to decide whether or not to participate. On the other hand, the good of society and the benefit of future patients suggest that the potential of developing effective treatments for acute brain injury justifies the use of some type of waiver of consent when the risk of the treatment is acceptably low.

To emphasize some of the problems of the current approaches to obtaining consent, the authors review literature suggesting that family members may not be truly impartial when asked to consent for an acutely injured loved one's participation. In emergency research because of their desire to grasp at any treatment that has even a slight chance of providing benefit. Also, it appears that many patients would not really want their family members to act as their surrogates in the first place.

In addition to reviewing these issues, the authors present the results of a survey of European neurotrauma centres. The results of the survey reinforce the points discussed by the authors.

After reading this article, one is inclined to agree with the authors conclusion that, under certain conditions, randomisation of patients into carefully evaluated and approved trials for treatment of traumatic brain Injury without the express consent of those patients is ethically justifiable.

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