Evidenced-based medicine and clinical practice guidelines for traumatic brain injury

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"After all, the concept of evidence based medicine is nothing more than *the state of mind that every clinical teacher hopes to develop in their students*"

D.Weatherall, 1997(14)

Just as coronary care has been described (3) in terms of four historical phases, so too can the recent history of the management of severe head injury be arbitrarily divided into at least four periods. The end of the first period took place in 1960 when Lundberg introduced intracranial pressure monitoring in the management of the neurosurgical patient (17). Before then, neurological examination was the main tool available to clinicians for evaluating and controlling the treatment of these patients. The second period can be characterized by the use of the CT scan for the diagnosis and follow-up of these patients and by the introduction of so-called "aggressive" management of severe head injury. Continuous ICP monitoring, the use of barbiturates, and hyperventilation are the main hallmarks of this period. The third phase was marked by the introduction of high-technology multimodality monitoring, beginning with SjO_2 and continuing with other modalities such as evoked potentials, near-infrared spectroscopy, Xenon-CT, and so on. The latest technologies which have been incorporated to this phase are brain tissue oxygen monitoring and microdialysis. This period coincides in time with what we consider to be the latest phase in the management of severe head injury, the so-called "evidence-based care". We can establish the beginning of this period in 1996 when the American Guidelines for the treatment for severe head injury were widely disseminated after their publication in the *Journal of Neurotrauma* (4).

A new philosophy of clinical practice: evidenced-based medicine

The application of traditional epidemiological concepts to clinical practice, gave birth a few years ago to a new discipline, so-called Evidence Based Medicine (EBM) (6). The term EBM was coined at McMaster Medical School in Canada in the eighties (24). According to this new philosophy, the practice and teaching of medicine must be based on knowledge of the evidence upon which clinical practice is based and on the strength of that evidence (6). Health authorities, purchasers and even our colleagues expect us to justify individual clinical decisions with explicit reference to evidence. Clinical decisions should ideally be based on high-quality systematic reviews, meta-analyses and randomized studies, although the reality is that perhaps as little as 10% of the care we provide can be based on this kind of hard evidence. This new way of thinking is specially relevant to the field of critical care medicine and in particular to the

management of severe head injury where state-of-the art technology and therapeutic strategies consume a large proportion of hospital budgets.

For many, this very expensive effort to improve the chances of survival of this particular group of patients, must be justified by a more accurate measurement of outcomes. Even the reliability of the methods we use to measure outcomes have been challenged many times and are still a continuous source of controversy. Two of the many questions to be answered are: 1) are we overusing expensive monitoring techniques which may not be useful? and 2) are we using unnecessary, sometimes useless and expensive therapies in the management of severe head injuries ?

The need to contain costs in the healthcare system is a problem in every developed country. For some, these monetary pressures on the healthcare system carry the implicit risk of contaminating and perverting the essence of evidence-based care. Cost-effectiveness analyses may have hidden agendas directed toward preventing further escalation of health care costs rather than toward improving the quality of care. For others, the future of clinical freedom is called into question with the implementation of evidence-based care.

Clinical practice guidelines and evidence-based medicine

The development of clinical practice guidelines has been a step forward in translating solid evidence into the day-to-day care of individual patients. Many of the controversial issues about guidelines are due to their definition. In a simple way and according to the Collins English Dictionary a Guideline is usually defined as *"a principle put forward to set standards or determine a course of action"* (15). Therefore, every protocol based on consensus or expert opinion was considered a guideline before the advent of evidence-based medicine. Guidelines, in this sense of the word, are not new in Medicine; different specialities have been involved in the design of guidelines for many years. What is new in this process is "the emphasis on systematic, evidence-based guidelines" (7). According to the definition given by the US Institute of Medicine, which pioneered the methodology behind clinical practice guidelines, this type of protocols are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (7).

The goals of clinical practice guidelines were well defined in the second book published by the Institute of Medicine in 1992 and can be summarized in the five following points: 1) assisting clinical decision making, 2) educating individuals or groups, 3) assessing and assuring the quality of care, 4)guiding allocation of resources and 5) reducing he risk of legal liability for negligent care (7). An additional advantage for clinicians is that guidelines help them to cope with the exponential increase in the number of clinical studies published.

Controversial issues in the development of guidelines for severe head injuries

The increasing acceptance of EBM by the medical community and the wide variability in the clinical management of severe head injuries, were the main reasons that led the charity, the Brain Trauma Foundation, to fund and support a task force to develop and disseminate evidence-based clinical practice guidelines for the management of severe head injury. Although this document was published by the Brain Trauma Foundation in 1995, it was widely disseminated among the neurosurgical and intensive care communities after its

publication in the November issue of the *Journal of Neurotrauma* in 1996 (4).

The publication of this document provoked important reactions in the neurosurgical community ranging from scepticism in some, to disappointment in others. The task force selected fourteen topics to be included in the first document. These topics were trauma system organization, treatment in initial resuscitation, blood pressure and oxygenation, indications for intracranial pressure (ICP) monitoring, ICP treatment threshold, ICP monitoring technology, cerebral perfusion pressure, hyperventilation, the use of barbiturates, steroids, critical pathway for treating intracranial hypertension, nutritional support, and the use of prophylactic anticonvulsant (5). Guidelines were developed using the Medline database exclusively for searching and finding relevant articles. All articles reviewed were classified into three different classes based on widely-used standardized criteria: class I, II and III studies. In Class I studies, only good quality prospective randomized controlled trials were included (4). Class II included those studies in which the data were collected prospectively or those retrospective studies in which reliable data were analyzed. In this last group observational studies, cohort studies, prevalence and case-control studies were included (4). In class III evidence, the authors of the Guidelines included studies based on retrospective analysis such as clinical series, databases or registries, case reviews, case reports, and expert opinion (4). According to the type of evidence available, recommendations were classified as standards, guidelines and options. *Standards* represent accepted principles of patient management that reflect a high degree of clinical certainty, *Guidelines* are recommendations based on moderate clinical certainty and *Options* are recommendations backed by Class III studies and therefore there is not enough clinical certainty to recommend them (4,5).

Many felt disappointment with the recommendations suggested by the task force in this important document. This feeling was because, surprisingly, only a few of the therapeutic manoeuvres routinely used in the management of the severely head injured patient, were backed by hard evidence. In this document, only three *standards* could be recommended: 1) that in the absence of increased ICP, chronic prolonged hyperventilation therapy should be avoided, 2) that glucocorticoids are not recommended for improving outcome or reducing ICP and that 3) prophylactic use of anticonvulsants is not recommended for preventing late posttraumatic seizures (4).

On the other hand, even the methods used by the task force to search for the relevant studies and to evaluate the external evidence necessary for answering clinically important questions, can be challenged. As an example, we can take the issue of whether to use glucocorticoids in the management of severe head injuries. For the Brain Trauma Foundation's guidelines, this is one of the few topics where the recommendation can be considered a *standard*. According to this document, glucocorticoids are not recommended in the management of severe head injury. However, in a systematic review published later by the Cochrane collaboration which analyzed the same topic, the conclusions were not the same (1). The Cochrane study, using a somewhat different methodology, concluded that although there is considerable uncertainty about the use of corticosteroids in acute traumatic brain injury, neither moderate benefits nor moderate harmful effects can be completely excluded (1). The authors of this study concluded that large clinical trials would be necessary to establish definitively whether or not the use of corticosteroids after traumatic brain injury is beneficial. Readers of both studies can extract different conclusions. For some, the uncertainty uncovered by the Cochrane collaboration and the high prevalence of head injury, would jus-

tify enrolling about 40000 patients in a clinical trial to discard moderate but clinically important effects of corticosteroids (2). For others, the results of both studies do not justify performing such a large trial (20).

These contradictory conclusions are puzzling, and for many put into question the methodology followed by some groups in the development of guidelines. The Cochrane collaboration uses more sophisticated tools in answering relevant issues. The differences affect both the methodology used in searching the relevant literature and also the criteria employed to select the most adequate randomized trials. Furthermore, their members apply meta-analytic methods to quantify the magnitude of differences (Summary odds-ratios). In general, the Cochrane collaboration perform more extensive literature searches using Medline, Embase, the Cochrane Library, other databases and registries and even handsearching without any language restriction. The different methodologies employed to develop practice guidelines can lead different groups to analyze different studies and, in turn, to extract different conclusions. As an example, the Brain Trauma Foundation's task force reviewed only 7 of the 14 clinical trials reviewed by the Cochrane collaboration (1).

The lesson to be learned from these two different analyses of the available evidence is that to avoid these pitfalls and inconsistencies, the definitions and methodology used in the development of guidelines must be standardized, widely disseminated and strictly followed by all groups involved in the development of evidence-based guidelines.

Evidence-based versus non-evidence based guidelines for head injuries

In the last four years, different "guidelines" have been developed by different groups producing somewhat different and sometimes conflicting and inconsistent documents. According to Servadei, head injury guidelines can be classified into 3 classes: evidence-based, pragmatic and nationally or locally adapted guidelines (25). Some critics of clinical practice guidelines have stated that these multiple and conflicting guidelines are an obstacle to improving care and that they create confusion in the medical community.

As an example of inconsistent recommendations in head injury guidelines, is the issue of the indications for intracranial pressure (ICP) monitoring in severely head injured patients. The use of ICP monitoring has been, and in some countries still is, a matter of considerable controversy. This is so, even though the results of the Traumatic Coma Data Bank have demonstrated beyond any reasonable doubt that the mortality and morbidity resulting from severe head injury are strongly related to raised ICP (19). In spite of all this evidence, Ghajar's study, published in 1995, showed that ICP monitoring was routinely used in the management of severe head injuries in only 28% of a randomly selected sample of Trauma centres in the United States (8). The continual controversy about ICP monitoring is mainly due to the fact that there is no randomized study that demonstrates that ICP monitoring improves the outcome of severe head injuries. But the question we should ask is: do we really need this study in 1999 ? or perhaps, as many have considered, would this type of study be unethical in the face of the considerable evidence we already have which shows that ICP is the main predictor of outcome in severe head injury.

Recently published guidelines face this problem of monitoring ICP in two different ways. The American evidence-based document, considers ICP monitoring to be a *guideline* and states that "ICP monitoring is appropriate in patients with severe head injury with an abnormal admission CT scan" (4). However, the

European Brain Injury Consortium's (EBIC) pragmatic guidelines (based on expert opinion), consider ICP monitoring "desirable" but not mandatory in severe head injury. Nevertheless, in contradicting that premise, the EBIC guidelines clearly suggest that "Treatment should not only be aimed at reducing ICP, but specially at restoring CPP to appropriate levels (60 - 70 mm Hg)" (18). Obviously, CPP cannot be controlled unless ICP is continuously monitored. The American evidence-based, and the EBIC pragmatic guidelines are an example of a different and sometimes contradictory approach to the same problem of monitoring.

To avoid confusion, clinical recommendations and protocols based on consensus or expert opinion should be differentiated from evidence-based guidelines. On the other hand, when the necessary evidence to support recommendations is inadequate or incomplete (16), it is much better to have evidence-based guidelines developed following strict methodologies than to have a few protocols based on expert opinion. Evidence-based recommendations can be improved as new evidence becomes available, while recommendations based on expert opinion or consensus are a continuous source of controversy and scepticism. As Jackson and Feder have stated *"Unless we can communicate a simple, pragmatic strategy for guideline development, we will continue to be embarrassed by variations in clinical guidelines as we are by inappropriate variation in clinical practice"* (16).

The grey areas of practice. What can we do in the absence of evidence?

Perhaps one of the most important problems in practising evidence-based care is the lack of evidence that justifies many of the treatments we use or that supports the utilization of most of the monitoring methods we routinely use in the management of severe head injuries. One of the most obvious examples that illustrates the dilemmas clinicians have to face is the appropriateness of routinely using invasive and expensive monitoring techniques in head–injured patients. For many, the regular use of these monitors would be only justified if they could provide additional information that could lead to clinical decisions that favourably affected the patient's outcome. Nevertheless, the care of the severely brain-injured patient is characterized by the fact that decisions about their management are frequently based on the use of multimodality monitoring techniques that often provide redundant information that is difficult to integrate in the management of these patients. Monitoring of oxyhaemoglobin saturation in the jugular bulb (SjO_2), arterio-jugular differences of lactates, near-infrared spectroscopy, brain tissue oxygen monitoring, and microdialysis are some of the methods we have at our disposal to monitor these patients at the bedside. If we consider that controversies still exist about the usefulness of ICP monitoring, what should the position of the clinician be when faced with the dilemma of using or not using some of these tools?

Almost all of the new methods available for monitoring brain-injured patients are directed to monitoring brain ischaemia. Even ICP is a variable that is used to calculate cerebral perfusion pressure (CPP) and therefore to protect the brain from ischaemia. But the question than can be asked is: if there is no evidence yet that these monitoring techniques improve the outcome, is it reasonable to incorporate so many expensive methods directed toward monitoring brain ischaemia ? Although for many of us the answer is affirmative, at the same time we have to admit that what we have right now to support this statement is based on indirect evidence. This indirect evidence suggests that ischaemia plays a very important role in increasing the morbidity and

mortality of the severely brain-injured patient.

The evidence we have about the role of ischaemia in head injuries comes from neuropathological and physiopathological studies. Graham et al. showed that ischaemic brain damage is present in about 90% of the patients who die after head injuries (11,13). It is also known that in many of these cases, ischaemic brain damage affected boundary vascular zones of the brain indicating that cerebral perfusion pressure was compromised when the patients were still alive (12,13). Additionally, from experimental and clinical studies we know that secondary ischaemia is involved in some of the most toxic neurochemical cascades that affect the brain after head injury. It has been well established that ischaemia increases extracellular levels of glutamate and that at the same time glutamate increases cytosolic-free calcium. Increases in intracelullar calcium is related to cell swelling, repetitive cell depolarization and cell death. But perhaps the most important data we have about brain ischaemia is information gathered in the last few years in patients with ischemic stroke that shows that around the central core of any severely ischemic tissue there is almost always a peripheral zone, generally nourished by collaterals, that is functionally altered but structurally viable (ischaemic penumbra) (26). Recent experimental data have shown that in ischaemic tissue there is a continuous recruitment of ischaemic penumbra into the infarction core (9,10). Therefore, it would be theoretically possible that adequate monitoring of ischaemic events in severe head injury could prevent the progression of the ischaemic brain into necrotic tissue. Although it is not yet known whether this hypothesis is reasonable, it is clear that to prevent this progression, appropriate monitoring of these patients is absolutely necessary to detect ischaemic events as soon as they appear.

An additional problem we have to keep in mind when asking for evidence that new monitoring technologies actually improve the outcome of these patients is the fact that the process of demonstrating efficacy in improving outcome of new monitoring techniques is usually a very difficult and slow one. On the other hand, evaluating the effects of new technologies on outcome is far more difficult than evaluating the effects of new therapeutic drugs (22). Apart from the obvious difficulties of doing randomized studies with monitors, the main problem to overcome, which usually acts as a confounder in these studies, is what is known as *learning contamination bias* (22). As Roizen and Toledano have stated, this bias is mainly due to the reality that *"even patients who may not benefit directly from new technology may benefit indirectly from what physicians learn by using it"* (22). This bias, based on the inescapable fact that physicians may learn from the act of monitoring itself, is very important and has implications for the design of those studies that assess new technologies (22). The only method available to completely avoid this bias and at the same time to demonstrate the effect of monitoring on outcome, the randomized clinical trial, does not in many cases completely control the confounding variables and in others, its use would be considered unethical.

A pragmatic approach to the monitoring dilemma

In the face of these difficulties, what we need is a pragmatic alternative approach to the problem. This type of approach to the new forms of monitoring in neurological critical care was, in our opinion, well defined by Ropper in 1985 in his editorial published in the Archives of Neurology (23). This paper was written when the debate about the usefulness of ICP monitoring in neurological critical care was

very hot. In his classical paper Ropper said that *"An ICP monitor-* for this you can read any monitor- *provides additional information that turns treatment from imperfect exercise to an individualized program that takes advantage of all pertinent physiological information" (23).* In times of evidence-based care, it is important to remark that monitors are only diagnostic tools that cannot improve the outcome of disease by themselves (21), and that severe head injury is no exception to this rule. To ask for evidence that monitors improve outcome is perhaps not the correct question. An alternative approach is to ask for accuracy, reliability and that the variable to be monitored has a well-demonstrated effect on outcome. If we use this approach, monitoring ICP, CPP and early detection of ischemic events is completely justified. On the other hand, multimodality monitoring is essential, as recent studies have shown, for the early diagnosis of many secondary events that occur after severe head injury, such as vasospasm, hyperaemia, ischaemia or brain swelling.

In addition to the above-mentioned points, we have to take into account that monitors are excellent tools for learning at the bedside. Furthermore, what we all learn by using these tools is, in our opinion, extremely helpful to the overall management of patients with a severe head injury. The early rejection of monitoring technology based on the lack of demonstrable benefit to outcome, carries the risk of blocking the learning process of physicians who use these technologies (22). It is important to emphasize that there is a natural and unavoidable process from research on new technology to the demonstration that this technology can modify outcome (22). Only time and adequately designed studies can prove that the rational use of some of these tools may improve the outcome of traumatic brain injury and may avoid the confounding effect of learning bias. Perhaps to ask for immediate evidence that new technologies improve the outcome, is to ask the wrong question at the wrong time.

As a last remark, neurosurgeons and intensive care specialists should adapt to the new times and educate themselves to be prepared to practice evidence-based medicine in the years to come. In a recent editorial published by Braunwald and Antman on evidenced-based coronary care, which can be applied to the management of severe head injury, these authors concluded by saying that *"…evidence-based coronary care will be more than just another phase in the evolution of coronary care; we believe that it is here to stay"* (3).

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