CURRENT INTERNATIONAL TRENDS IN SEVERE ACUTE BRAIN TRAUMA

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ABSTRACT - A comprehensive review is presented on current international trends regarding research and management of severe acute brain trauma. Controversial issues are thoroughly discussed and an attempt is made to clarify questionable aspects from pertinent publications in the international literature. A proposition is made to manage not only intracranial pressure and perfusion pressure, but also cerebral hemometabolic parameters in these critically ill patients. Currently available management guidelines are not evidence-based.

KEY WORDS: head injury, intracranial pressure, cerebral perfusion pressure, cerebral extraction of oxygen

Tendências internacionais atuais em traumatismo cerebral agudo grave

RESUMO - Uma revisão abrangente é apresentada referente a tendências internacionais atuais em pesquisa e tratamento do traumatismo cerebral agudo grave. Aspectos controversos são discutidos, e é feita tentativa de esclarecer pontos questionáveis da literatura internacional pertinente. Uma proposição e feita para que sejam tratados nao somente a pressão intracraniana e a pressão de perfusão cerebral, mas também parâmetros hemometabólicos cerebrais nestes pacientes gravemente enfermos. Normas ("guidelines") atualmente disponíveis para tratamento não são baseadas em evidência.

PALAVRAS-CHAVE: traumatismo cerebral, pressão intracraniana, pressão de perfusão cerebral, extração cerebral de oxigênio.

Over the past decade, conflicting information has been addressed with regard to research and management of severe acute brain trauma, so that heterogeneous standards for acute patient care have become apparent. With the exception of life-saving measures at the prehospital and emergency room levels, which are believed standardized in most developed and developing countries, diverse strategies have been reported in the intensive care unit setting.

This review is aimed at discussing and clarifying findings that have been reported in the pertinent international literature, as an attempt to guide neuroprofessionals toward better understanding clinical research and management propositions, insofar as neuro critical care is concerned.

Intracranial pressure and cerebral hemometabolism

In addition to the presence of acute intracranial lesions with mass effect (most of them promptly managed surgically), intracranial pressure (ICP) problems during intensive care have been frequently attributed to the presence of brain edema and subarachnoid hemorrhage. Despite ongoing research over the years, however, little is known about the influence of changes in cerebral blood volume (CBV). Nevertheless, cerebral blood flow (CBF) is directly proportional to CBV, and several studies have addressed variable CBF patterns during the acute phase of injury.

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Perhaps the most informative paper from the 1980s[1] addressed a statistically significant association between cerebral hyperemia and intracranial hypertension, in contrast with predominantly reduced CBF during periods of normal ICP. In this latter report[1], hyperemia was also described as normal CBF levels (in absolute values), which were nevertheless associated with decreased global cerebral oxygen extraction, as measured by the arteriojugular oxygen content difference ($AVDO_2$); that is, the finding of relative cerebral hyperperfusion with normal CBF was clear because cerebral oxygen consumption was pathologically reduced, and not only high but also normal CBF levels were associated with low oxygen extraction. From our findings[1], global cerebral ischemia was essentially ruled out in severe acute brain trauma.

In contrast, the Richmond group[2] later addressed a 33% rate of early global brain ischemia in 35 patients with severe acute brain trauma, during the first 6 hours after injury. However, despite CBF values in the low range, $AVDO_2$ did not exceed the upper normal limit of 8.3 vol%[3] in any of the studied patients (Figure 1 of Bouma's paper[2]). Therefore, the true rate of "pre-ischemic" or "potentially ischemic" levels of cerebral oxygen extraction was zero percent. In contrast, starting at approximately 12 postinjury hours, relative cerebral hyperperfusion represented a general rule *throughout the acute phase*, as determined by $AVDO_2$ values below the lower normal limit of 5.1 vol%[3] (Table 1 of that paper[2]). Unlike our previous report[1], in the Richmond series[2] no emphasis was placed on ICP problems relative to CBF and $AVDO_2$.

We[4] later reported that $AVDO_2$ is an unreliable parameter of cerebral oxygen extraction in either moderate or profound acute anemia, and proposed a new variable termed *cerebral extraction of oxygen* (CEO_2, the arteriojugular oxyhemoglobin saturation difference[4-8]). Moderate acute anemia is frequent during intensive care and is not managed under several circumstances. $AVDO_2$ underestimates cerebral oxygen extraction while CEO_2 does not. Therefore, $AVDO_2$ overestimates cerebral hyperemia (unlike CEO_2)[4]. Accordingly, therapeutic modalities for elevated ICP based on cerebral vasoconstriction (hyperventilation, dihydroergotamine, indomethacin, barbiturates, hypothermia, etc) can be optimized based on CEO_2 more accurately than by $AVDO_2$. The same applies to therapies that simultaneously lower the ICP and increase cerebral venous oxygenation and CBF, such as mannitol[6].

Cerebral perfusion pressure

First proposed by Langfitt et al.[9], cerebral perfusion pressure (CPP, the difference between mean arterial pressure and mean ICP) has been "re-visited" by Rosner et al.[10]. These latter authors have proposed managing acute brain trauma with the head flat, normocapnic throughout the acute phase, with induced arterial hypertension as a means of maintaining CPP above 70 mm Hg. Except for mannitol and cerebrospinal fluid drainage, none of the above-mentioned therapies was adopted in Rosner's experience[10].

As described above, however, relative cerebral hyperperfusion (rather than ischemia) represents a general rule during most of the acute postinjury phase and, therefore, cerebral vasoconstrictive therapies are indicated, in addition to mannitol. Rosner's claim of improved clinical outcome[10] was not valid because a control group was not evaluated. Rather, Rosner et al.[10] calculated chi-square outcome statistics using their patient population against that of the American Traumatic Coma Data Bank. The two populations were not comparable, however, because in Rosner's series only 35% of the patients had brain swelling, with a low 16% rate of compromised basilar cisterns, indicative of a less severe patient population than that of the coma bank.

A recent report[11] involving over 400 patients has made it clear that CPP levels above 60 mm Hg are not associated with improved clinical outcome, and that intracranial hypertension (rather than CPP) is the most devastating phenomenon in association with poor outcome figures. Furthermore, Rosner's patients underwent an average 18-day of ICP and CPP monitoring (with a 29% mortality rate)[10], versus one week only (with a low 9% mortality rate) in our large series[12] of over 350 prospectively evaluated, selected patients with high ICP and brain swelling, in whom therapeutic

measures were adopted to normalize not only ICP and CPP, but also CEO_2. Therefore, Rosner's proposal[10] induces intracranial hypertension, with resulting ultra-prolonged monitoring and high mortality rate relative to the presence of acutely decreased cerebrospinal fluid spaces.

From the above discussion, "CPP management" totally ignores the natural history of cerebral hemodynamics and metabolism in severe acute brain trauma; that is, a state of initially reduced CBF normally coupled with reduced cerebral oxygen consumption, which is then followed by a prolonged, sustained pattern of relative cerebral hyperperfusion. Furthermore, we[13] have also unequivocally demonstrated that normal-to-increased CPP holds absolutely no correlation with cerebral oxygen metabolism (both oxygen extraction and consumption), thus ruling out any beneficial effect of normal-to-increased CPP levels[13]. Accordingly, "CPP management" as previously proposed[10] involves more deleterious than beneficial effects both on intracranial dynamics and clinical outcome.

Combined cerebral oxygen and glucose metabolism

Back in 1995, we[8] reported a state of global cerebral hypoglycolysis during near normocapnia (when ICP problems had subsided); that is, cerebral extraction of glucose was pathologically reduced relative to CEO_2, a condition that markedly improved during optimized hyperventilation (which simultaneously normalized ICP, CEO_2 and cerebral extraction of glucose)[8].

In a later report, however, Bergsneider et al.[14] addressed cerebral hyperglycolysis also during near normocapnia. This "hypermetabolic" condition, however, was a function of a methodological artifact, because the ratio of cerebral glucose to oxygen consumption was calculated using cortical glucose values against global oxygen measurements. Yet, it is well known that global metabolic values are far lower than cortical ones.

Cerebral blood flow alone

In the normal (awake) monkey brain[15], ischemic CBF thresholds have been addressed at levels below 18 mL/100g/min. In comatose patients, however, cerebral oxygen consumption frequently falls by approximately 50% (or more) [16]. Accordingly, ischemic CBF thresholds in comatose patients are expectedly 50% lower than in the normal brain, or 9 mL/100g/min[17]. Therefore, research involving regional or global CBF alone in comatose patients has emphatically overemphasized cerebral ischemia without the necessary concomitant metabolic data [18-21]. In this respect, regional CBF values as high as 40 mL/100g/min have been proposed as "ischemic" in acute coma[21], an approach that appears to be conceptually inadequate.

Optimized versus indiscriminate hyperventilation

Optimized hyperventilation has been proposed in our work[7,8,12] as a means of not only normalizing ICP but also CEO_2. By doing so, we have introduced intentional restoration of the clinically beneficial coupling between CBF and oxygen consumption. In this respect, a previous study by Jaggi et al.[16] addressing observational (non interventional) research has disclosed better clinical outcome of patients when global cerebral oxygen extraction is spontaneously found within the normal range than when relative cerebral hyperperfusion (decreased oxygen extraction) exists during the acute postinjury phase.

In a recent prospective, controlled trial involving a large number of patients, we[12] have addressed statistically better clinical outcome figures in patients subjected to both moderate and profound optimized hyperventilation (based on CEO_2 monitoring), than in the control group where only mild non optimized hyperventilation was adopted (because CEO_2 monitoring was not adopted).

In contrast to the above findings, Muizelaar et al.[22] have addressed adverse effects of hyperventilation, but in a small group of patients randomly assigned to hypocapnic treatment. In this latter report, however, only 14% of the patients had elevated ICP when hyperventilation was initially instituted (Table 1 of that paper[22]). Accordingly, hyperventilation was contraindicated in as many as 86% of the randomized patients; that is, hyperventilation was used indiscriminately. These "adverse

effects" were described as a "slowness" in neurologic recovery which, nevertheless, was no different from the control group at one year postinjury.

Because of the small number of patients in those randomized groups[22], only 5-6 patients with more severe lesion types (e.g., diffuse axonal injury) could have well explained the observed "slowness" in neurologic recovery (typical of axonal injury), rather than an adverse effect of hyperventilation itself. Moreover, the mortality rate was 18% higher in non hyperventilated patients, which corresponds to approximately half the mortality rate reported by others[1,10,23]; that is, Muizelaar et al.[22] did not hyperventilate patients at random even in the presence of elevated ICP and progressing signs of tentorial herniation (in order not to violate the randomization scheme) when, in fact, half of those who died could have been saved if hyperventilated.

As previously reported[7,8], optimized hyperventilation presents with the very largest number of positive physiologic effects in comparison with any other treatment modality for acute brain injury with intracranial hypertension. These positive effects are as follows: 1) prompt normalization of elevated ICP[7]; 2) normalization of decreased CEO_2 (or relative hyperperfusion), thereby restoring normal coupling between CBF and oxygen consumption[7]; 3) normalization of pathologically decreased cerebral extraction of glucose[8]; 4) restoration of normal coupling between cerebral oxygen and glucose extraction, thereby restoring normal cerebral aerobic metabolism[8]; 5) normalization of CPP without the need for vasopressor drugs[7,8]; and 6) improvement or maintenance of adequate systemic hemodynamics and oxygenation[7]. These multiple positive physiologic effects explain the recently reported findings of improved clinical outcome in optimally hyperventilated patients in comparison with a control group[12].

Optimized mannitol

Also based on CEO_2 monitoring, optimization of mannitol administration has become possible[6]. In this latter report, we described a simultaneous decrease in elevated ICP and normalization of increased CEO_2 (or cerebral oligemia). Accordingly, in light of these findings, mannitol cannot be optimized based on ICP measurements only[6]; that is, mannitol is not optimally administered when high ICP is associated with decreased CEO_2 (relative hyperperfusion), because mannitol further increases CBF. This latter finding may explain a "rebound" effect, when ICP recurrently increases shortly after mannitol administration.

Optimized barbiturate therapy

Unlike optimized hyperventilation and mannitol[6-8,12], barbiturate (pentobarbital) therapy has been reported in association with transiently decreased cerebral venous oxygenation in some patients with refractory ICP[24]. These undesired findings were addressed shortly following the intravenous bolus injections, when the blood pressure fell. Accordingly, a transient decrease in cerebral oxygenation to oligemic hypoxic levels may be observed following barbiturate boluses, even though no adverse effects have been found during prolonged barbiturate maintenance infusion.

Additional therapies

In light of the above-described findings, it is apparent that virtually all therapeutic modalities for elevated ICP may be optimized by CEO_2 monitoring rather than by ICP and CPP only. This is particularly true because most therapies influence CBF and/or oxygen metabolism. Future studies will tell us more about that.

Alternative monitoring modalities

Stocchetti, et al.[25] have proposed bilateral jugular monitoring, as they found side-to-side differences of up to 15%. In their experience, however, continuous fiberoptic jugular monitoring was not carried out with strict immobilization of the patient's neck, so that much of their described differences may have been artifactual. This is because the fiberoptic jugular catheter may easily generate artifactual readings even with minor changes in head positioning. In light of improved

clinical outcome from a large series of patients subjected to unilateral continuous fiberoptic jugular monitoring[12], it is therefore apparent that bilateral jugular catheterization should not be considered.

Non invasive near infrared spectroscopy for mixed arteriolar and venular monitoring is being abandoned because, unlike the normal brain[26], this technique fails to demonstrate large hypoxic changes in jugular oxyhemoglobin saturation in injured brains[27]. This limitation is probably because the technology assumes normal arteriolo-venular compartmental distribution in injured brain, which may not be true under several circumstances.

Highly invasive, acutely implanted probes into brain tissue have also been proposed for both tissue oxygen monitoring and evaluation of other elements by microdialysis[28]. In this respect, however, acutely implanted brain tissue probes (even the smallest ones) produce focal microvascular compression and distortion, besides blood-brain barrier alterations. Therefore, artifactual abnormalities such as low tissue oxygen and high tissue lactate may be found[28], which may have no relationship with the rest of the brain that is not under mechanical load. Accordingly, it is also likely that brain tissue probes will soon be abandoned, at least by those who acknowledge their inherent technical limitations.

From the above discussion, unilateral jugular monitoring still represents the gold standard for bedside cerebral hemometabolic monitoring and management. For regional evaluation, however, CBF alone is not adequate, because concomitant metabolic information is always mandatory in injured brain. In this respect, out of the intensive care unit techniques are therefore required, such as positron emission tomography and/or functional magnetic resonance imaging. These two latter diagnostic modalities, however, are not suitable for acutely ill, unstable patients, to whom the intensive care unit still represents the most protective environment.

GUIDELINES

Back in 1996, guidelines for the management of severe acute brain trauma were reported and said to be evidence-based[29]. Those authors claimed that hyperventilation should be avoided and that normocapnic "CPP management"[10] should be adopted. As described above, however, *optimized hyperventilation*[7,8] was reported *before* those guidelines were written. Because optimized hyperventilation provides the largest number of positive physiologic effects in comparison with any other therapeutic modality[7,8], it then becomes clear that those guidelines[29] *are not* evidence-based.

Furthermore, normocapnic "CPP management"[10] is contraindicated in patients with acutely decreased cerebrospinal fluid spaces under most circumstances, as outlined above. As of 1998, combined management of ICP, CPP and CEO_2 by optimized hyperventilation (besides other therapies) has been clearly reported in association with improved clinical outcome[12]. It therefore remains for future, alternative guidelines to fully cover the pertinent literature in an unbiased fashion, so that true evidence-based information may become available to those involved in neuro critical care medicine.

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