Increased brain tissue oxygen tension in children with traumatic brain injury using temperature-corrected guided ventilation during prophylactic hypothermia

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ABSTRACT

Objective: To investigate whether ventilatory management using a temperature-corrected (pH-stat) or uncorrected (alpha-stat) blood gas analysis strategy improves brain tissue oxygen tension ($PbrO_2$) in children prophylactically treated with moderate hypothermia for traumatic brain injury.

Design, setting and participants: Double crossover study conducted in the intensive care unit of a tertiary children's hospital. Nine children aged 3–14 years with severe traumatic brain injury were randomly allocated twice to a 6-hour period of either alpha- or pH-stat management while being kept hypothermic at 32.5°C.

Main outcome measures: $PbrO_2$, intracranial pressure (ICP) and $PbrO_2/PaO_2$.

Results: $PbrO_2$ was significantly higher during pH-stat management (alpha-stat, 23.2 mmHg [95% CI, 22.4–24.0 mmHg] v pH-stat, 28.7 mmHg [95% CI, 27.9–29.5 mmHg]; $P < 0.001$). $PbrO_2/PaO_2$ was significantly higher during pH-stat (alpha-stat, 0.190 [95% CI, 0.187–0.193] v pH-stat, 0.251 [95% CI, 0.246–0.259]; $P < 0.05$). ICP was non-significantly higher during pH-stat (alpha-stat, 8.8 mmHg [95% CI, 8.1–9.5 mmHg] v ph-stat,10.2 mmHg [95% CI, 9.6–10.8]).

Conclusion: $PbrO_2$ may be improved using a pH-stat blood gas management strategy in prophylactic hypothermia for paediatric patients with traumatic brain injury without any clinically relevant increase in ICP.

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Some recent studies and reviews suggest that early and prophylactic hypothermia may improve the outcome of patients with traumatic brain injury (TBI), although this remains controversial and debated in the literature.[1-5] The role of hypothermia in severe brain injury is to control intracranial pressure (ICP), reduce brain tissue metabolism, limit reperfusion injury, and reduce the inflammatory response after injury.[4]

Management of TBI consists of optimising cerebral blood flow and oxygen delivery to the injured brain without raising ICP.[6,7] ICP can be controlled with sedation, muscle paralysis, mannitol, hypothermia and mild hyperventilation.[8] However, hyperventilation has not been associated with improved outcome and is not recommended.[9]

Devices have become available to measure brain tissue oxygen pressure ($PbrO_2$) directly.[10-13] It has been shown that interstitial tissue oxygenation changes mirror changes in cerebral blood flow, indicating that a change in the balance between local oxygen delivery and local oxygen demand is occurring.[13-15] The relationship between ICP, brain temperature, $PaCO_2$ and pH is an important aspect of brain injury management.[16]

The primary regulator of vasomotor tone in the cerebral vasculature is believed to be the extracellular pH of the vascular smooth muscle.[17] As bicarbonate is the only significant buffer in the cerebrospinal fluid, and as the highly diffusible carbon dioxide (CO_2) molecule can readily penetrate the blood–brain barrier, $PaCO_2$ represents the principal determinant of brain extracellular pH.

Normal ranges for pH and $PaCO_2$ are only defined at a body temperature of 37°C. Blood gases measured in the laboratory at 37°C are termed alpha-stat, whereas blood gases corrected to the patient's actual temperature are termed pH-stat. For example, a mechanically ventilated, hypothermic patient with a body temperature of 28°C may have a $PaCO_2$ of 40 mmHg when blood gas is measured at 37°C. However, this value would be reported as 25 mmHg when corrected to 28°C. The pH would be 7.52 and the clinician might be inclined to modify ventilation to normalise $PaCO_2$ and pH. This would create a relative respiratory acidosis. Most of the experience with alpha- or pH-stat management originates from induced hypothermia for prophylactic brain protection during cardiopulmonary bypass. Based on physiological arguments, pH-stat should be preferable to alpha-stat,[17] but neither approach has shown to achieve a better outcome.[18]

Limited data are available for alpha- versus pH-stat-based management in TBI. Animal research and a small human study in stroke patients demonstrated that pH-stat control is superior to alpha-stat.[19] Recently, Vigue and colleagues reported the relationship between ICP and temperature-corrected $PaCO_2$ in patients with TBI[16] using alpha-stat

management, and found that with hypothermia and constant minute volume ventilation, patients became hypocapnic and their ICP decreased. The effect of decreased ICP disappeared once the patients became normocapnic (mimicking a pH-stat approach).

We hypothesised that while using prophylactic hypothermia in children with TBI, pH-stat management improves brain tissue oxygen tension.

Methods

We performed a randomised double crossover study of children with TBI during prophylactic moderate hypothermia to investigate the effect of pH-stat or alpha-stat blood gas management on brain tissue oxygen tension. The study was conducted in the intensive care unit of Mater Children's Hospital, Brisbane, Queensland.

The study was approved by the Mater Health Services Human Research Ethics Committee (approval no. 707C). Nine children with severe TBI were enrolled into the study after informed written consent was obtained from a parent or guardian.

Patients were enrolled within the first 24 hours after injury. Inclusion criteria were children with a Glasgow Coma Scale score $\leqslant 8$, an abnormal computed tomography (CT) scan, or a normal CT scan and posturing, intubated and ventilated, and fulfilling institutional criteria for ICP monitoring. In our unit, we routinely use intraparenchymal monitoring with a multichannel probe providing measurements of ICP, brain temperature (BrTemp) and brain tissue oxygen tension ($PbrO_2$) (LICOX GMS, Kiel, Germany and Camino, San Diego, Calif, USA). We excluded children with suspicion of brain death, existing ventriculoperitoneal or ventriculoatrial shunts or a pre-existing neurological disorder.

In our unit, it is standard practice to manage TBI with prophylactic moderate hypothermia (32.5°C) for at least 48 hours using a Blanketrol II cooling mattress (Cincinnati Sub-Zero, Cincinnati, Ohio, USA). The standard treatment protocol for TBI further includes mechanical ventilation aiming for a $PaCO_2$ of 35 mmHg, muscle paralysis, sedation with a continuous infusion of morphine and midazolam, prophylactic phenytoin if an intracranial haemorrhage is evident, maintenance of serum sodium at 145 mmol/L, and brain function monitoring using the LICOX system inserted into the less affected cerebral hemisphere. Cerebral perfusion pressure (CPP) is maintained at an age-specific level using noradrenaline and dobutamine[20-22] to control arterial blood pressure. ICP > 20 mmHg is treated with sedation, additional paralysis, thiopentone infusion, and hypertonic fluids such as mannitol 20% (0.5 g/kg) or 3% saline (5 mL/kg).

Children were only enrolled into the study once stable conditions of the brain injury management were achieved 24 hours after admission. A pH- or alpha-stat blood gas management strategy was used randomly for 6 hours, followed by the alternative management in a crossover design. In alpha-stat management, $PaCO_2$ was kept at 35 mmHg assuming a body temperature of 37°C, and in the pH-stat, using the patient's actual body temperature. $PaCO_2$ levels of 35 mmHg were achieved by titrating the minute volume. End-tidal CO_2 monitoring was used as a guide to monitor trends of CO_2 levels avoiding too frequent blood gas analysis.

The primary outcome parameter was $PbrO_2$. Secondary outcome parameters were ICP, CPP and the number of interventions used to treat elevated ICP or reduced CPP such as a sedation bolus, fluid bolus, inotropic support, hypertonic fluids (20% mannitol or 3% saline) or thiopentone treatment.

For continuous parameters such as mean arterial pressure, ICP and CPP, a value was obtained from the clinical information system every 15 minutes. Blood gases were obtained as clinically required.

Statistical analysis

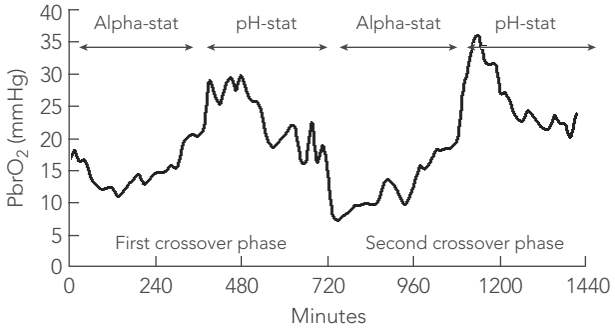
For continuous parameters such as $PbrO_2$, ICP and CPP, a linear mixed model was used, adjusting for factors such as alpha- or pH-stat management and covariates such as arterial CO_2 tension and time of measurement. To compare interventions in each study period an analysis of variance (ANOVA) test was used with a Bonferroni correction for repeated measurements. Data are presented as mean (SE). All analyses were performed using SPSS, version 15.0 (IBM, Armonk, NY, USA).

Results

Nine children (4 girls, 5 boys) fulfilling the inclusion criteria were enrolled; they had a mean age of 7.3 years (SE, 1.4 years) and body weight of 26.6 kg (SE, 4.2 kg). None of the patients died during the study period. All patients showed signs of global injury-related changes on the initial CT; three patients showed additional focal lesions such as intraparenchymal blood that did not need to be drained or had a space-occupying effect. None of the patients had seizures before admission or during the study period (based on clinical observations, as electroencephalogram monitoring was not available). A complete dataset was obtained for all patients, with information from 18 pH-stat and 18 alpha-stat management periods.

While on the pH-stat management, significantly more fluid boluses (0.9% saline) were received than while on alpha-stat management ($P = 0.03$, ANOVA). No differences

Figure 1. Change of brain tissue oxygen tension during alpha-stat and pH-stat periods



were found in the number of interventions administered such as sedation boluses, mannitol or 3% saline boluses and no differences were found for the amount of background sedation (midazolam and morphine), thiopentone, noradrenaline or dobutamine administered.

Figure 1 shows a representative $PbrO_2$ recording for the two crossover phases. Table 1 shows the summarised measured physiological parameters for both crossover phases whereas the figures show the values obtained for each phase individually.

The $PbrO_2$ was significantly higher ($P < 0.001$, general mixed linear model) during both pH-stat crossover periods than during alpha-stat, with the second phase of the crossover showing the highest $PbrO_2$ values (Figure 2). The general mixed model showed that the time of measurement did not affect $PbrO_2$, except for an adaptation of cerebral perfusion to a change in $PaCO_2$ level. The $PbrO_2$/PaO_2 ratio was significantly higher during pH-stat management ($P < 0.05$) (Table 1).

Within each of the management strategies, there was no association found between $PbrO_2$ and $PaCO_2$, except that the achieved $PaCO_2$ level affected $PbrO_2$.

ICP values were similar during both management periods, with a slight trend towards higher ICP levels during pH-stat, but this was not statistically significant (Figure 3). Within each of the management strategies there was a significant association between $PaCO_2$ and ICP level ($P < 0.001$). CPP was overall higher during alpha-stat management, with the greatest difference found in the first phase of the study ($P < 0.001$) (Figure 4). Within each of the blood gas management strategies, there was a significant association between $PaCO_2$ and CPP ($P < 0.001$).

Table 1. Summarised pooled physiological parameters for both crossover phases

	Alpha stat (95% CI)	pH stat (95% CI)
$PbrO_2$, mmHg	23.2* (22.4–24.0)	28.7* (27.9–29.5)
$PbrO_2/PaO_2$	0.190* (0.187–0.193)	0.251* (0.246–0.259)
Alpha-stat $PaCO_2$, mmHg	38.3* (37.2–39.4)	42.5* (41.5–43.5)
pH-stat $PaCO_2$, mmHg	30.9* (30.0–31.8)	33.9* (32.7–35.1)
ICP, mmHg	8.8 (8.1–9.5)	10.2 (9.6–10.8)
CPP, mmHg	71.9* (70.4–73.4)	68.5* (67.1–69.9)
MAP, mmHg	80.3 (78.9–81.7)	78.6 (77.0–80.2)
Brain temperature, °C	32.4 (32.3–32.5)	31.8 (31.6–32.0)

CCP = cerebral perfusion pressure. ICP = intracranial pressure. MAP = mean arterial pressure. $PbrO_2$ = brain tissue oxygen tension.
* Significant difference for repeated measurements using analysis of variance (ANOVA) with Bonferroni correction ($P < 0.05$).

Discussion

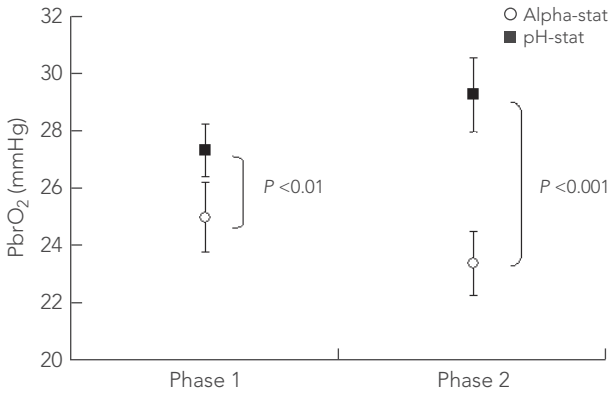
In our study, a pH-stat management strategy significantly increased brain tissue oxygen tension in children with severe TBI who were treated with prophylactic hypothermia. We showed an average increase of about 20% using a pH-stat management strategy, a change that potentially could be clinically significant and change outcome.

TBI remains the leading cause of death and disability in children,[23] accounting for more than 50% of all childhood deaths.[24] Despite impressive progress in paediatric intensive care management over the past two decades, the outcome of children with severe TBI remains unfavourable.[25]

There has been much debate over hypothermia versus normothermia for the management of TBI and the discussion is ongoing.[26] Basic science studies of hypothermia as a neuroprotective measure after TBI have shown a great deal of promise.[27] It is speculated that hypothermia reduces the metabolism and the oxygen demand of the injured brain. Hence, titration of brain tissue oxygen delivery to meet demand is tempting. $PbrO_2$ can be increased by increasing the inspired oxygen fraction, but this strategy has the disadvantage of increased oxygen toxicity to the lungs. Cerebral blood vessels are responsive to changes in $PaCO_2$. Hence, it is possible to manipulate $PaCO_2$ to achieve higher $PbrO_2$ without the disadvantage of increased ICP. One mechanism to achieve this uses pH-stat ventilation management in order to adjust the arterial CO_2 level to the patient's actual body temperature. Our study investigates the effect of pH-stat management on $PbrO_2$ in TBI. Despite the relatively small number of patients investigated, the effect of pH-stat management was significant and could affect long-term outcome and neurodevelopment of children with TBI.

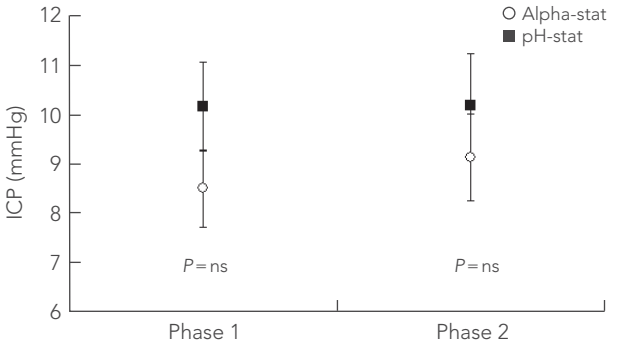
Hyperventilation of patients with severe brain injury is associated with a transient decrease of ICP and $PbrO_2$.[10] This strategy is considered controversial.[9] pH-stat manage-

Figure 2. Brain tissue oxygen tension ($PbrO_2$) (95% CI) during pH- and alpha-stat management



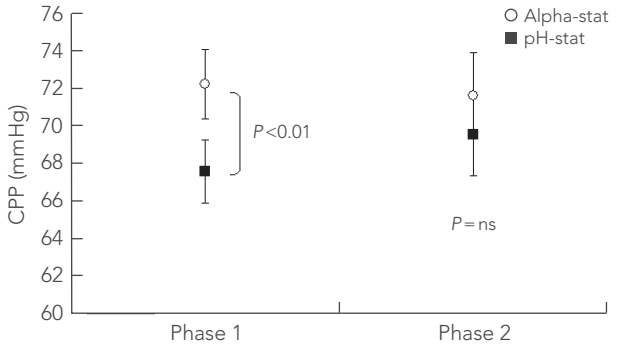
During both phases, pH-stat management improved $PbrO_2$ significantly compared with alpha-stat management.

Figure 3. Change in intracranial pressure (ICP) (95% CI) during pH- and alpha-stat management



ICP did not change during either management period.

Figure 4. Change of cerebral perfusion pressure (CCP) (95% CI) during pH- and alpha-stat management



CCP was significantly higher during alpha-stat in the first phase but not during the second phase of the crossover study.

ment causes hypoventilation, with an increase of arterial CO_2, in comparison with alpha-stat management. An increase of ICP due to cerebral vasodilatation and increase of $PbrO_2$ should occur. Indeed, in our study, ICP increased slightly with a pH-stat strategy, but this did not reach statistical significance, in comparison to the improved brain oxygenation. The CO_2 reactivity of the injured brain changes in the first few days after trauma. The first 24 hours after trauma are characterised by a decreased CO_2 reactivity, followed by increased reactivity on Days 2–5 after injury. Our data suggest a similar behaviour of the CO_2 reactivity, with a greater impact of blood gas management in the second phase of the crossover design, indicating that the CO_2 reactivity increases over time after injury. During pH-stat management, patients showed a higher $PbrO_2$ during the second phase than in the first phase. This could potentially be related to changes in CO_2 reactivity.

Recent TBI guidelines suggest that maintaining a $PbrO_2$ level > 25 mmHg may improve outcome.[15,28] In the current study, this threshold was achieved in the pH-stat but not in the alpha-stat strategy. Furthermore, the pH-stat approach allowed a significantly improved $PbrO_2/PaO_2$ ratio. A pH-stat approach improved $PbrO_2$ while less injurious ventilatory support with lower inspired oxygen fraction was offered. A recent study by Kollmar and colleagues showed an improved cerebral blood flow with a pH-stat management in patients with large ischaemic strokes treated by hypothermia.[19]

The clinical management during alpha- and pH-stat periods was very similar, except that more fluid boluses were needed during the pH-stat period. This may be explained by the peripheral vasodilatation that may occur with slightly increased arterial PCO_2.

Some limitations concerning the interpretation of the $PbrO_2$ measurements need to be discussed. The polargraphic oxygen-sensitive electrode used in our study averages the $PbrO_2$ values from the region in which the probe was placed. In our study, the probe was normally placed in the non-affected or less affected frontal lobe.

The number of patients studied is small, but the treatment effect could have already been demonstrated. Outcome data for the patients are not demonstrated and were not part of the initial protocol. Such data need to be obtained in a larger randomised controlled trial with neurodevelopmental outcome measures. Although recent trials have shown little or no benefit of prophylactic hypothermia in TBI, our results may apply for the treatment of refractory increased ICP with hypothermia.[5]

Conclusions

$PbrO_2$ may be improved by using a pH-stat blood gas management strategy in patients with severe TBI treated by moderate hypothermia without the disadvantage of increased ICP.

Competing interests

None declared.

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