Special review

Indomethacin - A Review of its Role in the Management of Traumatic Brain Injury

R. G. ROBERTS*, J. W. REDMAN†
**Critical Care Directorate, University Hospital of Wales, Cardiff, UNITED KINGDOM*
†Critical Care Directorate, St Georges Hospital, London, UNITED KINGDOM

ABSTRACT

Objective: *To review the use of indomethacin in the management of traumatic brain injury.*

Data sources: *Articles reported from 1966 to 2001 and identified through a MEDLINE search of the English language literature on the use of indomethacin in traumatic brain injury.*

Summary of review: *Traumatic brain injury (TBI) is a frequent cause of mortality and morbidity in patients with head injury. The use of indomethacin in treating raised intracranial pressure (ICP) secondary to TBI is controversial. Clinical studies suggest that it may be useful in the management of intracranial hypertension, when used in combination with standard techniques, by decreasing cerebral blood flow and reducing ICP during the restoration of the blood brain barrier. Its unique mechanism of action may be due to precapillary vasoconstriction, which reduces the transcapillary transfer of fluid into the cerebral extracellular space. However, large, prospective, randomised and controlled studies have not yet been performed to confirm its benefit in patients with TBI.*

Conclusions: *Indomethacin should only be considered as an experimental therapy for refractory intracranial hypertension in TBI patients, as current evidence is not available to support its routine use in the management of an elevated ICP. Its use in patients with cerebral vasospasm, renal failure, bleeding disorders, peptic ulceration and coagulopathies is contraindicated.* (**Critical Care and Resuscitation 2002; 4: 271-280**)

Key words: Indomethacin, traumatic brain injury, intracranial hypertension, precapillary vasoconstriction, non-steroidal anti-inflammatory drugs

The use of indomethacin for treatment of increased intracranial pressure (ICP) secondary to brain trauma is controversial and largely the result of anecdotal evidence and small clinical trials. It is currently considered an experimental treatment for raised ICP in head injured patients where conventional therapy has failed.

High ICP and low cerebral perfusion pressure (CPP) are prognostic factors correlating to a poor outcome in patients with traumatic brain injury (TBI).[1-3] In one study, impaired vasoreactivity to hyperventilation in combination with a raised ICP correlated with a poor outcome with a mortality/vegetative state/severe disability rate of almost 100%.[1] Recent estimates have shown that 70 - 80% of patients with severe head injuries have intracranial hypertension,[1-4] which, when combined with a low CPP, may be an important determinant of poor outcome. Aggressive treatment of raised ICP in TBI has been shown in some studies to reduce mortality.[4-10] Currently, new clinical trials are concentrating on a reduction of hydrostatic capillary pressure and restitution of plasma colloid osmotic pressure to improve outcome. Thus treatment of intracellular

Correspondence to: Dr.R.G. Roberts, Critical Care Directorate, University Hospital of Wales, Cardiff, CF14 4XW, United Kingdom. (e-mail: richroberts@doctors.org.uk)

oedema by managing the disturbances of brain volume regulation caused by disruption of the blood brain barrier (BBB) has been a focus of recent therapeutic strategies. We examined indomethacin's role and the evidence for its beneficial effect in patients with TBI and raised ICP.

Pathophysiology of traumatic brain injury

The brain has little energy reserve and an increase in cerebral metabolism and oxygen consumption results in an increase in cerebral blood flow (CBF) and oxygen delivery. Cerebral blood flow is altered by a change in arterial carbon dioxide tension, although it is relatively constant over a wide range of arterial oxygen tensions and CPP due to cerebral autoregulation (figure 1).

Cerebral perfusion pressure may be represented by the equation,

$$CPP = MAP - ICP$$

and cerebral blood flow may be represented by the equation,

$$CBF = \frac{CPP}{CVR}$$

Where,

CPP = cerebral perfusion pressure
MAP = mean arterial pressure
ICP = intracranial pressure
CBF = cerebral blood flow
CVR = cerebral vascular resistance

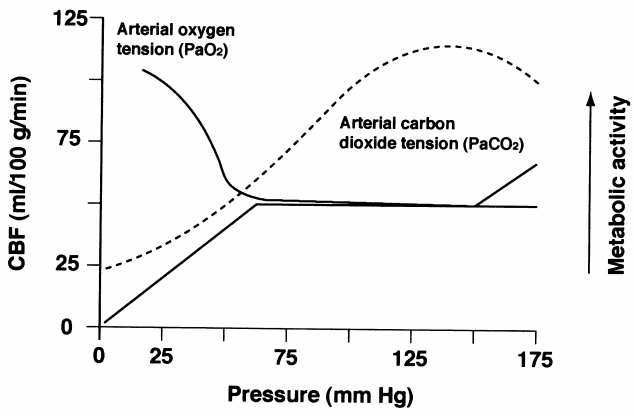

Figure 1. Normal cerebral blood flow responses to arterial oxygen, arterial carbon dioxide and perfusion pressure changes

Traumatic brain injury can be caused by primary or secondary cerebral lesions. Primary cerebral lesions describe those lesions that occur at impact and are due to direct head trauma or indirect injury caused by acceleration/deceleration inertial forces. The lesions include diffuse axonal damage (caused by shearing forces), expanding mass lesions and dural tears. Secondary cerebral lesions describe ischaemic lesions that are caused by hypoxia, hypotension or metabolic abnormalities associated with the head trauma. These injuries are potentiated by seizures and elevated body temperatures.[9-11] Ischaemic brain damage due to a decrease in CBF results from either a decrease in CPP and/or an increase in CVR. Estimates of post traumatic cerebral vasospasm vary from 5 - 35% in severe head injury[12,13]

As the brain is contained in a closed vault it is sensitive to any increase in intracerebral volume. The 'Monro-Kellie doctrine' states that the incompressible structures within the cranial vault are in a state of volume equilibrium and any increase in the volume of one component (i.e. blood, cerebrospinal fluid or brain tissue) must be compensated for by a decrease in volume of one or more of the other components.[14,15] A small increase in volume may lead to a dramatic increase in ICP leading to a decrease in CPP and eventually brain ischaemia (figure 2). The reduction in CBF caused by cerebral oedema causes cerebral hypo-xia stimulating cerebral vasomotor activity, resulting in an increase in MAP and increase in CBF. However, there is a limit to the maintenance of CBF by increasing MAP. If ICP continues to rise CBF will ultimately fall.

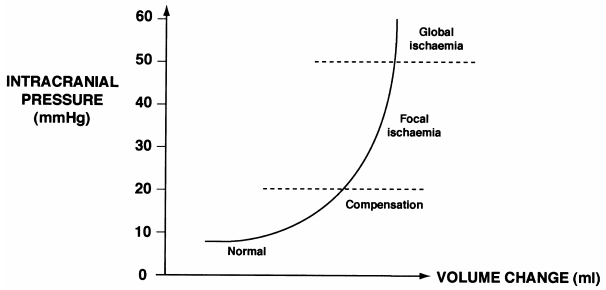

Figure 2. Change in intracranial pressure with change in intracranial volume, and pressures at which focal and global cerebral ischaemia occur.

Specific goals have been advocated for the treatment of head injuries. For example, ICP < 20 mmHg, CPP > 70 mmHg and maintenance of cerebral oxygen extraction at 24 - 42%. Non-surgical methods used to treat an increase in ICP include hyperventilation,[16] osmotherapy,[17] hypothermia, sedation and metabolic depressant drugs.[18]

However, while hypocapnic cerebral vasoconstriction decreases cerebral blood volume and therefore ICP,[16] in prospective randomised studies, prolonged hyperventilation has been shown to have adverse effects on outcome in patients with TBI,[12,19] and is now only

recommended for the temporary management of intracranial hypertension.[13]

Osmotic agents establish osmotic gradients across the BBB to draw water from the intracranial compartment and lower ICP.[17] Also, barbiturate coma has been recommended in patients who have refractory intracranial hypertension by reducing cerebral metabolism ($CMRO_2$) and, in turn, CBF.[13,18] However, there are currently no prospective, randomised placebo-controlled trials that have confirmed the value of these agents in reducing mortality in patients with TBI.

As the BBB becomes more permeable in patients with TBI, brain oedema may be exacerbated by an increase in CPP.[20-22] Accordingly, the view that post traumatic cerebral hyperaemia may be deleterious in TBI has led some investigators to use indomethacin in the management of these patients.

Possible beneficial actions of indomethacin in traumatic brain injury

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic activity via a reversible inhibition of cyclo-oxygenase. The mechanisms whereby indomethacin reduces CBF are not fully understood but are thought to include, a decrease in production of cerebral vasodilating prostaglandins (via cyclo-oxygenase inhibition), mild hyperventilation (decreasing $PaCO_2$) and direct vasoconstriction of cerebral blood vessels.[23-27] The effects of indomethacin on cerebrospinal fluid (CSF) production and body temperature have also been investigated, although it appears that its major effect arises in the unique effects on the cerebral circulation not observed with other NSAIDs such as ibuprofen, diclofenac, naproxen or sodium salicylate.[28-31] This is supported by evidence that the blood-brain barrier is almost impermeable to indomethacin, with a brain tissue/plasma concentration ratio of 0.02.[32] Pial vessels and larger cerebral arteries are either unaffected or vasodilate with indomethacin.[33-36] There is also no angiographic evidence that indomethacin causes spasm of the internal carotid artery or major intracranial vessels.[37,38]

In other studies, indomethacin has been shown to have no effect on cerebral metabolism,[36,39-43] cerebral autoregulation[2,7] and cerebral hyperaemia caused by hypoxia,[44] hypoglycaemia,[45] bicuculline-induced seizures,[46] or transient cerebral ischaemia.[47]

Pharmacology and pharmacokinetics of indomethacin

Indomethacin is available in oral, rectal and intravenous (i.v.) formulations. In one study of healthy adults, peak plasma concentrations were reached within 5 minutes of i.v. dosing, whereas with oral dosing, peak plasma concentrations were reached after 30 - 120 minutes.[48] Similar to oral dosing, rectal administration resulted in 100% bioavailability but the rate of absorption was slower.

Indomethacin is approximately 90% bound to circulating albumin[49] and therefore has poor CSF penetration.[32,50] Decreased albumin levels have been documented following head injury and may contribute to higher unbound indomethacin concentrations leading to higher CSF concentrations.[51]

Indomethacin is metabolised in the liver to glucuronide conjugates, which are excreted via renal and biliary routes with a significant enterohepatic circulation contributing to a large reported range in the plasma half-life (i.e 1 - 16 hr).[49]

The common side effects associated with indomethacin include headache, dizziness, vertigo and fatigue, and while confusion, depression, convulsions, depersonalisation and tinnitus have also been documented they are often transient and disappear with continued use or with reduction in dosage. Indomethacin can also cause a significant reduction in renal function, decreasing glomerular filtration rate and urine output. It may precipitate acute renal failure, particularly in patients with a decreased extracellular volume or reduced renal perfusion, by inhibiting the production of vasodilating renal prostaglandins and allowing unimpeded vasoconstriction by circulating angiotensin and catecholamines. Sodium and water retention, interstitial nephritis and hyperkalaemic hyporeninaemic hypo-aldosteronism have also been documented as a result of the administration of indomethacin. Accordingly, indomethacin should be used carefully in critically ill patients (although, there have been some reports of no increase in renal insufficiency in patients without head injury).[52,53]

Gastrointestinal complications may also occur with nausea, vomiting and dyspepsia found in 3 - 9% and rectal bleeding found in less than 1%. Two studies have recorded no increase in peptic ulceration in critically ill adults receiving NSAIDs,[52,53] and no significant effect on mean bleeding time after a single oral dose of 50 mg or an iv infusion of 25 mg.[54,55] However, increases in bleeding times have been recorded with multiple oral or i.v. doses of indomethacin,[54,56,57] although one study reported no clinical signs of abnormal bleeding.[57]

The effect of indomethacin on bleeding time is due to inhibition of platelet thromboxane production, reversibly binding to platelet cyclo-oxygenase causing an anti-aggregatory effect.[58] However, as the enzyme is reversibly inhibited, the duration of the antiplatelet effect is short and disappears within 48 hrs, with platelets recovering 44% of their pre-treatment thromboxane production levels one day after indomethacin discontin-

uation (an effect that is more rapid than acetylsalycilic acid where recovery of thromboxane production is only 7.3%, 24 hours after one 100 mg dose of aspirin).[59]

The effect of indomethacin on intracranial pressure

a) *Cerebral blood flow*

In TBI an increase in CBF is associated with an increase in ICP,[60,61] although initially (for the first few hours at least), cerebral blood flow decreases.[62] Thereafter, CBF increases and may lead to intracranial hypertension,[25,63-65] and sometimes "malignant brain oedema".[63,66] Studies have demonstrated a decrease in CBF following administration of indomethacin in the rat,[67-69] gerbil,[70] rabbit,[71,72] cat,[73,74] dog,[75] goat,[76] primate,[37,77-80] pig[81] and normal humans.[39,40,82-90]

In controlled studies on human volunteers,[85,87,88,90,91] indomethacin dosing regimes have not been uniform, ranging from 25 - 100 mg orally to 0.4 mg/kg intravenously. While it may be difficult to compare these studies, a significant and consistent decrease in CBF in response to indomethacin is often found (table 1). In most studies, the effect on CBF begins 0.5 - 1 min following an intravenous dose and peaks at approximately 5 - 30 minutes, indicating that the effect is rapid and possibly due to a direct action.[77,81]

Table 1. Cerebral blood flow change with indomethacin administration

Authors	Patient Number	CBF (mL/100g/min)	% change
Pickles *et al*[85]	6	81.6 → 60.7	25
Therkelsen *et al*[87]	29	(60 - 62) → (39 - 40)	33 - 37
Jensen *et al*[90]	60	(65 - 68) → (44 - 48)	26 - 35
Jensen *et al*[91]	29	(45 - 80) → (24 - 57)	33 - 40

CBF = cerebral blood flow

Recent trials indicate that patients with TBI and intracranial hypertension who have impaired CO_2 reactivity[2,17] have a poor prognosis, with conventional non-surgical therapies often being ineffective.[1-3,92] In these patients indomethacin may be useful.[40,93] Concerns regarding the induction of cerebral ischaemia due to precapillary vasoconstriction in patients with TBI and a high ICP, have led some to recommend jugular bulb oximetry monitoring, and that treatment should be limited to those with high venous O_2 saturation (i.e. > 60%) and/or a relatively high CBF (i.e. > 40mL/100g/min).[40,94]

b) *Cerebrospinal fluid production*

Shalk *et al*,[95] also postulated that indomethacin might lower ICP by indirectly decreasing CSF production by potentiating the inhibitory effect of endothelin on CSF production by the choroid plexus.

c) *Body temperature*

Hyperthermia occurring in head injury is not uncommon,[96] and the brain is very sensitive to temperature changes during periods of raised ICP[97] and ischaemia.[98-100] Indomethacin may therefore be neuroprotective by lowering cerebral temperature and therefore ICP[40] by preventing hyperpyrexia.[101]

Clinical studies of indomethacin in traumatic brain injury

Post traumatic brain oedema is common[102] and will contribute to a raised ICP. The blood-brain barrier is also altered with an increased permeability leading to a disturbance in the normal mechanisms regulating the normal brain volume and inducing cerebral oedema.[103-105]

This hypothesis has led to studies investigating hydrostatic pressure and colloid osmotic pressure control of cerebral volume. By manipulating blood pressure and precapillary vasoconstriction, the "Lund protocol"[103,106] using β antagonists, α_2 agonists, precapillary vasoconstriction and negative fluid balances has been used in an attempt to reduce ICP in patients with TBI. In an interim analysis of a study using this protocol, Asgeirsson *et al* reported 9 survivors in 11 patients,[103] compared with 100% mortality in a group of patients treated by conventional therapy in identical entry criteria controls.[1-3]. Indomethacin, as a cerebral precapillary vasoconstrictor, has also been studied in patients with head injury.

Jensen *et al*,[40] treated 5 patients aged between 22 and 42 years of age with severe head injuries and elevated ICP. All patients received hyperventilation to an average $PaCO_2$ of 25.5 mmHg (3.4 kPa) and received phenobarbitone and mannitol. If the ICP was > 20 mmHg for more than 1 hr, the patient was hyperventilated and the phenobarbitone infusion was increased to 2 g/day. Indomethacin was then given as a bolus of 30 mg i.v. followed by an infusion at 30 mg/hr when ICP was elevated above 20 mmHg for 1 - 2 hours despite standard therapy. The CBF was measured at baseline, 15 min, 2 hr, 4 hr and 7 hr during the infusion. Treatment began on the 2nd or 3rd day following TBI and was continued for 7 hr. The ICP decreased within 5 - 10 seconds of the indomethacin injection and reached a minimum level within 1 - 5 minutes. The average ICP fell from 28 mmHg before treatment to 17 mmHg 15 minutes after the bolus, and stayed < 20 mmHg for 5 hr in all patients. The CBF decreased from 34 to 25

mL/100g/min 2 hours after initiation of treatment and remained low at 7 hr in three patients. The $CMRO_2$ and lactate/oxygen index, a common indicator of ischaemia, remained stable during treatment and unchanged from pre-treatment levels. The arteriovenous lactate difference increased 15 minutes following the bolus but was not significantly different from pre-treatment levels for the duration of the treatment period. The rectal temperature decreased from 38°C to 37.3°C.

However, there are a number of problems with this study. It involved a small number of patients, was non-randomised and uncontrolled. It also lacked specific information regarding concurrent interventions, limiting its usefulness in extrapolating the results to routine clinical practice.

Biestro *et al*,[107] treated an elevated ICP in 10 patients with TBI and one patient with spontaneous sub-arachnoid haemorrhage. The goals of therapy were an ICP < 20 mmHg and a CPP 70 - 80 mmHg. All patients received mannitol 0.25 mg/kg and thiopentone infusions. A bolus of indomethacin 50 mg i.v. over 20 minutes was followed by an infusion of 21.5 $\pm$ 11.4 mg/hr over 30 $\pm$ 9 hr. One hour after the bolus dose, the ICP decreased significantly from 34.4 mmHg to 16.4 mmHg and remained low (23.1 mmHg) during the course of the infusion until the end of the treatment period. The CPP increased significantly after the bolus from 67 to 76 mmHg but was not significantly different at the end of treatment. Some rebound of the ICP occurred after cessation of the infusion (e.g. 27.3 mmHg to 31.8 mmHg or a 38% increase) although this was not accompanied by a change in the CPP. There were no cases of cerebral ischaemia or infarction on follow up CT scan.

However, the small sample size of the study, its lack of ICP data during the course of the infusion and lack of information about specific co-interventions also limited the usefulness of this report.

Dahl *et al*,[108] performed a prospective observational study in 14 head-injured patients to compare the effects of intravenous indomethacin with hyperventilation. The goals of therapy were to decrease the ICP to < 20 mmHg and CPP to > 70 mmHg. All patients were mechanically ventilated to a $PaCO_2$ of 30 - 34 mmHg (4 - 4.5 kPa). Mannitol or barbiturates were not used. Patients received a bolus of 30 mg of indomethacin i.v., and, after 20 minutes, reductions in median ICP and CBF and an increase in CPP were observed. The clinical outcome at 6 and 12 months was assessed using the Glasgow outcome score with 13 of 14 patients at 6 months, and all patients at 12 months, classified as having a good outcome. This trial demonstrated that indomethacin was effective in reducing ICP in severe head injured patients without causing cerebral ischaemia. The deficiencies of the trial include lack of randomisation and blinding, a small sample size, minimal information concerning co-interventions, lack of utilisation of other gold standard therapies and the inclusion of patients without refractory increased ICP. Other case reports that have reported a reduction in ICP with indomethacin include: Clemmensen *et al*,[109] who reported the use of intravenous indomethacin in an acute liver failure patient with raised ICP with boluses of 25 mg, Hansen *et al*,[110] who reported the use of indomethacin boluses of 30 mg i.v. to control raised ICP in a patient following resection of a large cerebral arteriovenous abnormality, Bundgaard *et al*,[111] who demonstrated effective reduction in ICP and CBF without a reduction in $AVDO_2$ using indomethacin in 9 patients having craniotomy for supratentorial cerebral

Table 2. Comparison of clinical studies using indomethacin in head injured patients

Authors	Design	No.	Treatment	ΔICP	ΔCPP	ΔCBF
Jensen, *et al*[40]	Case series	5	30mg iv then 30mg/hr for 7 hr	28 → 17 ($p < 0.05$)		34 → 25 ($p < 0.05$)
Biestro, *et al*[107]	Case series	10	50mg i.v infusion 30 hr	34.4 → 16.4 ($p < 0.05$)	67.0 → 76.4 ($p < 0.05$)	
Dahl, *et al*[108]	P.Obs	14	30mg bolus	15.0 → 9.4 ($p < 0.001$)	73.8 → 81.0 ($p = 0.001$)	39 → 30 ($p = 0.001$)
Clemmensen, *et al*[109]	Case report	1	25mg i.v boluses	↓		
Hansen, *et al*[110]	Case report	1	30mg i.v boluses	↓		
Bungaard, *et al*[111]	Case series	9		↓	↑	
Imberti, *et al*[112]	Case report	1	5-10mg i.v boluses	68.0 → 22.7	↑	

P.Obs = prospective, observational study, No. = number of patients, ΔICP = change (mmHg) in mean intracranial pressures, ΔCPP = change (mmHg) in mean cerebral perfusion pressures, ΔCBF = change (mmHg) in mean cerebral blood flows.

tumours, and Imberti *et al*,[112] who demonstrated the bolusing of 5 - 10 mg indomethacin i.v. in a 3 year-old patient following severe brain trauma was effective in treating raised ICP (68.1 mmHg $\pm$ 0.8 mmHg to 22.7 $\pm$ 5.6) and was associated with a rise in SjO_2 (suggesting global CPP was improved as a result of reduced ICP). All reports are summarised in table 2.

CONCLUSION

Indomethacin is a pharmacological alternative for the management of refractory ICP elevation in severe head injury.[1-3] Despite the inherent weaknesses of the current clinical trials, there is a consistent reduction in ICP by 37 - 52%, a reduction in CBF of 22 - 26% with an increase in CPP by 14% without any reported adverse effects.[31,40,107,109,110,112]

However, concerns relating to indomethacin induced cerebral ischaemia caused by reducing CBF are real. Both Jensen *et al*,[40] and Dahl *et al*,[108] demonstrated CBF < 20 mL/100g/min with $SjvO_2$ < 50%, although there was no recorded detrimental outcome, possibly indicating that ischaemia may not be the main inducer of cerebral oedema.

The mechanism of action of indomethacin in reducing CBF and ICP is not fully understood. If it is due to cerebral artery precapillary vasoconstriction then the reduction in extracellular oedema may be due to a reduction in the effect of the TBI disruption of the BBB.

It appears that indomethacin will probably be used only in those patients with TBI in whom a raised $SjvO_2$ (> 75%) is found, although data concerning this indication is still relatively unconvincing. Data regarding the best route of administration is also currently lacking although the intravenous route would appear to be ideal. Its use in patients with cerebral vasospasm, renal failure, bleeding disorders, peptic ulceration and coagulopathies is contraindicated and may limit its use in the critically ill patient.

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REFERENCES

1. Schalen W, Messeter K, Nordstrom CH. Cerebral vasoreactivity and the prediction of outcome in severe traumatic brain lesions. Acta Anaesthesiol Scand 1991;35:113-122.
2. Nordstrom CH, Messeter K, Sundbarg G, Schalen W, Werner M, Ryding E. Cerebral blood flow, vasoreactivity, and oxygen consumption during barbiturate therapy in severe traumatic brain lesions. J Neurosurg 1988;68:424-431.
3. Messeter K, Nordstrom CH, Sundbarg G, Algotsson L, Ryding G. Cerebral hemodynamics in patients with acute severe head trauma. J Neurosurg 1986;64:231-237.
4. Miller JD, Becker DP, Ward JD, Sullivan HG, Adams WE, Rosner MJ. Significance of intracranial hypertension in severe head injury. J Neurosurg 1977;47:503-516.
5. Miller JD, Butterworth JF, Gudeman SK, et al. Further experience in the management of severe head injury. J Neurosurg 1981;54:289-299.
6. Levin HS, Saydjari C, Eisenberg HM, et al. Vegetative state after closed-head injury. A Traumatic Coma Data Bank Report. Arch Neurol 1991;48:580-585.
7. Jones PA, Andrews PJ, Midgley S, et al. Measuring the burden of secondary insults in head-injured patients during intensive care. J Neurosurg Anesthesiol 1994;6:4-14.
8. Saul TG, Ducker DB. Effect of intracranial pressure monitoring and aggressive treatment on mortality in severe head injury. J Neurosurg 1982;56:498-503.
9. Saul TG, Ducker TB.Intracranial pressure monitoring in patients with severe head injury. Am Surg 1982;48:477-480.
10. Ruff RM, Marshall LF, Crouch J, et al. Predictors of outcome following severe head trauma: follow-up data from the Traumatic Coma Data Bank. Brain Inj 1993;7:101-111.
11. Borel C, Hanley D, Diringer MN, Rogers MC. Intensive management of severe head injury. Chest 1990;98:180-189.
12. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. Neurosurg 1991; 75:731-739.
13. Bullock R, Chesnut RM, Clifton G, et al. Guidelines for the management of severe head injury. Brain Trauma Foundation. Eur J Emerg Med 1996;3:109-127.
14. Monroe A. Observations on the structure and Function of the Nervous system, Edinburgh: Creech & Johnson, 1783.
15. Kellie G. An account of the appearances observed in the dissection of two of three individuals presumed to have perished in the storm of the 3D, and whose bodies were discovered in the vicinity of Leith on the morning of the 4th of November 1821 with some reflections on the pathology of the brain. Trans Med Chir Sci Edinb 1824;1:84-169.
16. Miller JD, Dearden NM, Piper IR, Chan KH. Control of intracranial pressure in patients with severe head injury. J Neurotrauma 1992;9 Suppl 1:S317-S326.
17. Muizelaar JP,Lutz HA 3rd, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. J Neurosurg 1984;61:700-706.
18. Eisenberg HM, Frankowski RF, Contant CF, Marshall LF, Walker MD. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. J Neurosurg 1988;69:15-23.

19. Lundberg N, Troupp H, Lorin H. Continuous recording of the ventricular-fluid pressure in patients with severe acute traumatic brain injury. A preliminary report. J Neurosurg 1965;22:581-90.
20. Asgeirsson B, Grande PO, Nordstrom CH. A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation. Intensive Care Med 1994;20:260-267.
21. Vollmer DG, Dacey RG Jr. The management of mild and moderate head injuries. Neurosurg Clin N Am 1991;2:437-455.
22. Miller JD. Vasoconstriction as head injury treatment--right or wrong? Intensive Care Med 1994;20:249-250.
23. Marmarou A, Maset AL, Ward JD, et al. Contribution of CSF and vascular factors to elevation of ICP in severely head-injured patients. J Neurosurg 1987;66:883-890.
24. Piper IR, Miller JD, Dearden NM, Leggate JR, Robertson I. Systems analysis of cerebrovascular pressure transmission: an observational study in head-injured patients. J Neurosurg 1990;73:871-880.
25. Chopp M, Welch KM, Tidwell CD, Knight R, Helpern JA. Effect of mild hyperthermia on recovery of metabolic function after global cerebral ischemia in cats. Stroke 1988;19:1521-1525.
26. Hardebo JE, Hanko J, Owman C. Species variation in the cerebrovascular response to neurotransmitters and related vasoactive agents. Gen Pharmacol 1983;14:135-136.
27. Kauser K, Rubanyi GM, Harder DR. Endothelium-dependent modulation of endothelin-induced vasoconstriction and membrane depolarization in cat cerebral arteries. J Pharmacol Exp Ther 1990;252:93-97.
28. Markus HS, Vallance P, Brown MM. Differential effect of three cyclooxygenase inhibitors on human cerebral blood flow velocity and carbon dioxide reactivity. Stroke 1994;25:1760-1764.
29. Uddman R, Goadsby PJ, Jansen I, Edvinsson L. PACAP, a VIP-like peptide: immunohistochemical localization and effect upon cat pial arteries and cerebral blood flow. J Cereb Blood Flow Metab 1993;13:291-297.
30. Simko A, Mardoum R, Merritt TA, Bejar R. Effects on cerebral blood flow velocities of slow and rapid infusion of indomethacin. J Perinatol 1994;14:29-35.
31. Eriksson S, Hagenfeldt L, Law D, Patrono C, Pinca E, Wennmalm A. Effect of prostaglandin synthesis inhibitors on basal and carbon dioxide stimulated cerebral blood flow in man. Gen Pharmacol 1983;14:179-180.
32. Baer JE, Hucker HB, Duggan DE. Bioavailability of indomethacin in man. Ann Clin Res 1974;6:suppl 11:44-47.
33. Vlahov V. Role of the prostaglandines in the regulation of the cerebral blood circulation. Agressologie 1975;16 Spec No B:31-34.
34. Wei EP, Ellis EF, Kontos HA. Role of prostaglandins in pial arteriolar response to CO2 and hypoxia. Am J Physiol 1980;238:H226-H230.
35. Pickard JD, Vinall PE, Simeone FA. Prostaglandins and cerebral vasospasm: a problem of interpretation. Surg Forum 1975;26:496-498.
36. Chapleau CE, White RP, Robertson JT. Cerebral vasospasm: effects of prostaglandin synthetase inhibitors in vitro. Neurosurgery 1980;6:155-159.
37. Pickard JD, MacDonell LA, MacKenzie ET, Harper AM. Response of the cerebral circulation in baboons to changing perfusion pressure after indomethacin. Circ Res 1977;40:198-203.
38. Walker V, Pickard JD. Prostaglandins, thromboxane, leukotrienes and the cerebral circulation in health and disease. Adv Tech Stand Neurosurg 1985;12:3-90.
39. Eriksson S, Hagenfeldt L, Law D, Patrono C, Pinca E, Wennmalm A. Effect of prostaglandin synthesis inhibitors on basal and carbon dioxide stimulated cerebral blood flow in man. Acta Physiol Scand 1983;117:203-211.
40. Jensen K, Ohrstrom J, Cold GE, Astrup J. The effects of indomethacin on intracranial pressure, cerebral blood flow and cerebral metabolism in patients with severe head injury and intracranial hypertension. Acta Neurochir (Wien) 1991;108:116-121.
41. McCulloch J, Kelly PA, Grome JJ, Pickard JD. Local cerebral circulatory and metabolic effects of indomethacin. Am J Physiol 1982;243:H416-H423.
42. White RP, Hagen AA. Cerebrovascular actions of prostaglandins. Pharmacol Ther 1982;18:313-331.
43. Dahlgren N, Rosen I, Nilsson B. The effect of indomethacin on the local cerebral blood flow increase induced by somato-sensory stimulation. Acta Physiol Scand 1984;122:269-274.
44. Sakabe T, Siesjo BK. The effect of indomethacin on the blood flow-metabolism couple in the brain under normal, hypercapnic and hypoxic conditions. Acta Physiol Scand 1979;107:283-284.
45. Dahlgren N, Rosen I, Nilsson B. The effect of indomethacin on the local cerebral blood flow increase induced by somato-sensory stimulation. Acta Physiol Scand 1984;122:269-274.
46. Ingvar M, Nilsson B, Siesjo BK. Local cerebral blood flow in the brain during bicuculline-induced seizures and the modulating influence of inhibition of prostaglandin synthesis. Acta Physiol Scand 1981;111:205-212.
47. Kagstrom E, Smith ML, Wallstedt L, Siesjo BK. Cyclo-oxygenase inhibition by indomethacin and recirculation following cerebral ischemia. Acta Physiol Scand 1983;118:193-201.
48. Alvan G, Orme M, Bertilsson L, Ekstrand R, Palmer L. Pharmacokinetics of indomethacin. Clin Pharmacol Ther 1975;18:364-73
49. Helleberg L. Clinical Pharmacokinetics of indomethacin. Clin Pharmacokinet 1981;6:245-258.
50. Rothermich NO. An extended study of indomethacin. I. Clinical pharmacology. JAMA 1966;195:531-536.
51. Bannwarth B, Netter P, Lapicque F, Pere P, Thomas P, Gaucher A. Plasma and cerebrospinal fluid concentrations of indomethacin in humans. Eur J Clin Pharmacol 1990;38:343-346.

52. Bernard GR, Reines HD, Halushka PV, et al. Prostacyclin and thromboxane A2 formation is increased in human sepsis syndrome. Effects of cyclooxygenase inhibition. Am Rev Respir Dis 1991;144:1095-1101.
53. Haupt MT, Jastremski MS, Clemmer TP, Metz CA, Goris GB. Effect of ibuprofen in patients with severe sepsis: a randomized, double-blind, multicenter study. The Ibuprofen Study Group. Crit Care Med 1991;19:1339-1347.
54. Buchanan GR, Martin V, Levine PH, Scoon K, Handin RI. The effects of "anti-platelet" drugs on bleeding time and platelet aggregation in normal human subjects. Am J Clin Pathol 1977;68:355-359.
55. Rorarius M, Miralles J, Baer GA, Palomaki E. Diclofenac versus indomethacin given as intravenous infusions: their effect on haemodynamics and bleeding time, and side-effects in healthy subjects. Ann Clin Res 1985;17:306-309.
56. Taivainen T, Hiller A, Rosenberg PH, Neuvonen P. The effect of continuous intravenous indomethacin infusion on bleeding time and postoperative pain in patients undergoing emergency surgery of the lower extremities. Acta Anaesthesiol Scand 1989;33:58-60.
57. Mattila MA, Ahlstrom-Bengs E, Pekkola P. Intravenous indomethacin or oxycodone in prevention of post-operative pain. Br Med J (Clin Res Ed) 1983;287:1026.
58. Rane A, Oelz O, Frolich JC, et al. Relation between plasma concentration of indomethacin and its effect on prostaglandin synthesis and platelet aggregation in man. Clin Pharmacol Ther 1978;23:658-668.
59. Walenga RW, Wall SF, Setty BN, Stuart MJ. Time-dependent inhibition of platelet cyclooxygenase by indomethacin is slowly reversible. Prostaglandins 1986;31:625-637.
60. Obrist WD, Langfitt TW, Jaggi JL, Cruz J, Gennarelli TA. Cerebral blood flow and metabolism in comatose patients with acute head injury. Relationship to intracranial hypertension. J Neurosurg 1984;61:241-253.
61. Minamisawa H, Smith ML, Siesjo BK. The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. Ann Neurol 1990;28:26-33.
62. Bouma GJ, Muizelaar JP, Stringer WA, Choi SC, Fatouros P, Young HF. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg 1992;77:360-368.
63. Bruce DA, Alavi A, Bilaniuk L, Dolinskas C, Obrist W, Uzzell B. Diffuse cerebral swelling following head injuries in children: the syndrome of "malignant brain edema". J Neurosurg 1981;54:170-178.
64. Muizelaar JP, Marmarou A, DeSalles AA, et al. Cerebral blood flow and metabolism in severely head-injured children. Part 1: Relationship with GCS score, outcome, ICP, and PVI. J Neurosurg 1989;71:63-71.
65. Imberti R, Bellinzona G, Ilardi M, Bruzzone P, Pricca P. The use of indomethacin to treat acute rises of intracranial pressure and improve global cerebral perfusion in a child with head trauma. Acta Anaesthesiol Scand 1997;41:536-540.
66. Schutta HS, Kassell NF, Langfitt TW. Brain swelling produced by injury and aggravated by arterial hypertension. A light and electron microscopic study. Brain 1968;91:281-294.
67. Pickard JD. Role of prostaglandins and arachidonic acid derivatives in the coupling of cerebral blood flow to cerebral metabolism. J Cereb Blood Flow Metab 1981;1:361-384.
68. McCulloch J, Kelly PA, Grome JJ, Pickard JD. Local cerebral circulatory and metabolic effects of indomethacin. Am J Physiol 1982;243:H416-H423.
69. Dahlgren N, Nilsson B, Sakabe T, Siesjo BK. The effect of indomethacin on cerebral blood flow and oxygen consumption in the rat at normal and increased carbon dioxide tensions. Acta Physiol Scand 1981;111:475-485.
70. Crockard A, Iannotti F, Ladds G. Cerebrovascular effects of prostaglandin inhibitors in the gerbil. J Cereb Blood Flow Metab 1982;2:67-72.
71. Bill A. Effects of indomethacin on regional blood flow in conscious rabbits--a microsphere study. Acta Physiol Scand 1979;105:437-442.
72. Hierton C. Effects of indomethacin, naproxen and paracetamol on regional blood flow in rabbits: a microsphere study. Acta Pharmacol Toxicol (Copenh) 1981;49:327-333.
73. Vlahov V. Role of the prostaglandines in the regulation of the cerebral blood circulation. Agressologie 1975;16 Spec No B:31-34.
74. Shigeno S, Fritschka E, Shigeno T, Brock M. Effects of indomethacin on rCBF during and after focal cerebral ischemia in the cat. Stroke 1985;16:235-240.
75. Ruszczewski P, Herbaczynska-Cedro K. Release of prostaglandin-like substances into cerebral venous blood in conditions injurious to brain in the dog. Acta Physiol Pol 1978;29:489-499.
76. Hoffman WE, Albrecht RF, Pelligrino D, Miletich DJ. Effects of prostaglandins on the cerebral circulation in the goat. Prostaglandins 1982;23:897-905.
77. Pickard JD, Mackenzie ET. Inhibition of prostaglandin synthesis and the response of baboon cerebral circulation to carbon dioxide. Nat New Biol 1973;245:187-188.
78. Pickard J, Tamura A, Stewart M, McGeorge A, Fitch W. Prostacyclin, indomethacin and the cerebral circulation. Brain Res 1980;197:425-431.
79. Harris RJ, Bayhan M, Branston NM, Watson A, Symon L. Modulation of the pathophysiology of primate focal cerebral ischaemia by indomethacin. Stroke 1982;13:17-24.
80. McCalden TA, Nath RG, Thiele K. The role of prostacyclin in the hypercapnic and hypoxic cerebrovascular dilations. Life Sci 1984;34:1801-1807.
81. Nilsson F, Bjorkman S, Rosen I, Messeter K, Nordstrom CH. Cerebral vasoconstriction by indomethacin in intracranial hypertension. An experimental investigation in pigs. Anesthesiology 1995;83:1283-1292.

82. Amano T, Meyer JS. Prostaglandin inhibition and cerebrovascular control in patients with headache. Headache 1982 Mar;22(2):52-9
83. Wennmalm A, Eriksson S, Hagenfeldt L, Law D, Patrono C, Pinca E. Effect of prostaglandin synthesis inhibitors on basal and carbon dioxide-stimulated cerebral blood flow in man. Adv Prostaglandin Thromboxane Leukot Res 1983;12:351-355.
84. Okabe T, Meyer JS, Amano T, Okayasu H, Mortel K. Prostaglandin inhibition and cerebrovascular hemodynamics in normal and ischemic human brain. J Cereb Blood Flow Metab 1983;3:115-121.
85. Pickles H, Brown MM, Thomas M, et al. Effect of indomethacin on cerebral blood flow, carbon dioxide reactivity and the response to epoprostenol (prostacyclin) infusion in man. J Neurol Neurosurg Psychiatry 1984;47:51-55.
86. Seideman P, von Arbin M. Cerebral blood flow and indomethacin drug levels in subjects with and without central nervous side effects. Br J Clin Pharmacol 1991;31:429-432.
87. Therkelsen K, Jensen KA, Freundlich M, Thorshauge H, Bunemann L, Bogeskov Nielsen L. Endothelin-1 and cerebral blood flow: influence of hypoxia, hypercapnia and indomethacin on circulating endothelin levels in healthy volunteers. Scand J Clin Lab Invest 1994;54:441-451.
88. Nitter WH, Johnsen LF, Eriksen M. Acute effects of indometacin on cerebral blood flow in man. Pharmacology 1995;51:48-55.
89. Kraaier V, Van Huffelen AC, Wieneke GH, Van der Worp HB, Bar PR. Quantitative EEG changes due to cerebral vasoconstriction. Indomethacin versus hyperventilation-induced reduction in cerebral blood flow in normal subjects. Electroencephalogr Clin Neurophysiol 1992;82:208-212.
90. Jensen K, Kjaergaard S, Malte E, Bunemann L, Therkelsen K, Knudsen F. Effect of graduated intravenous and standard rectal doses of indomethacin on cerebral blood flow in healthy volunteers. J Neurosurg Anesthesiol 1996;8:111-116.
91. Jensen K, Freundlich M, Bunemann L, Therkelsen K, Hansen H, Cold GE. The effect of indomethacin upon cerebral blood flow in healthy volunteers. The influence of moderate hypoxia and hypercapnia. Acta Neurochir (Wien) 1993;124:114-119.
92. Cold GE, Jensen FT, Malmros R. The cerebrovascular CO2 reactivity during the acute phase of brain injury. Acta Anaesthesiol Scand 1977;21:222-231.
93. Grande PO. The effects of dihydroergotamine in patients with head injury and raised intracranial pressure. Intensive Care Med 1989;15:523-527.
94. Cold GE, Jensen K, Bundgaard H, Astrup J, Bergholt B. Treatment of intracranial hypertension with indomethacin. Anesthesiology 1996;85:1499-1501.
95. Schalk KA, Faraci FM, Heistad DD. Effect of endothelin on production of cerebrospinal fluid in rabbits. Stroke 1992;23:560-563.
96. Clifton GL, Robertson CS, Grossman RG, Hodge S, Foltz R, Garza C. The metabolic response to severe head injury. J Neurosurg 1984;60:687-696.
97. Duhaime AC, Ross DT. Degeneration of hippocampal CA1 neurons following transient ischemia due to raised intracranial pressure: evidence for a temperature-dependent excitotoxic process. Brain Res 1990;512:169-174.
98. Chopp M, Welch KM, Tidwell CD, Helpern JA. Global cerebral ischemia and intracellular pH during hyperglycemia and hypoglycemia in cats. Stroke 1988;19:1383-1387.
99. Minamisawa H, Nordstrom CH, Smith ML, Siesjo BK. The influence of mild body and brain hypothermia on ischemic brain damage. J Cereb Blood Flow Metab 1990;10:365-374.
100. Busto R, Dietrich WD, Globus MY, Valdes I, Scheinberg P, Ginsberg MD. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. J Cereb Blood Flow Metab 1987;7:729-738.
101. Benedek G, Toth-Daru P, Janaky J, Hortobagyi A, Obal F Jr, Colner-Sasi K. Indomethacin is effective against neurogenic hyperthermia following cranial trauma or brain surgery. Can J Neurol Sci 1987;14:145-148.
102. Miller JD. The management of cerebral oedema. The management of cerebral oedema. Br J Hosp Med 1979;21:152-161.
103. Asgeirsson B, Grande PO, Nordstrom CH. A new therapy of post-trauma brain oedema based on haemodynamic principles for brain volume regulation. Intensive Care Med 1994;20:260-267.
104. McClain CJ, Hennig B, Ott LG, Goldblum S, Young AB. Mechanisms and implications of hypoalbuminemia in head-injured patients. J Neurosurg 1988;69:386-392.
105. Todd NV, Graham DI. Blood-brain barrier damage in traumatic brain contusions. Acta Neurochir Suppl (Wien) 1990;51:296-299.
106. Eker C, Asgeirsson B, Grande PO, Schalen W, Nordstrom CH. Improved outcome after severe head injury with a new therapy based on principles for brain volume regulation and preserved microcirculation. Crit Care Med 1998;26:1881-1886.
107. Biestro AA, Alberti RA, Soca AE, Cancela M, Puppo CB, Borovich B. Use of indomethacin in brain-injured patients with cerebral perfusion pressure impairment: preliminary report. J Neurosurg 1995;83:627-630.
108. Dahl B, Bergholt B, Cold GE, Astrup J, Mosdal B, Jensen K, Kjaersgaard JO. CO(2) and indomethacin vasoreactivity in patients with head injury. Acta Neurochir (Wien) 1996;138:265-273.
109. Clemmesen JO, Hansen BA, Larsen FS. Indomethacin normalizes intracranial pressure in acute liver failure: a twenty-three-year-old woman treated with indomethacin. Hepatology 1997;26:1423-1425.
110. Hansen PA, Knudsen F, Jacobsen M, Haase J, Bartholdy N. Indomethacin in controlling "normal perfusion pressure breakthrough" in a case of large cerebral arteriovenous malformation. J Neurosurg Anesthesiol 1995;7:117-120.

111. Bundgaard H, Jensen K, Cold GE, Bergholt B, Frederiksen R, Pless S. Effects of perioperative indomethacin on intracranial pressure, cerebral blood flow, and cerebral metabolism in patients subjected to craniotomy for cerebral tumors. J Neurosurg Anesthesiol 1996;8:273-279.

112. Imberti R, Bellinzona G, Ilardi M, Bruzzone P, Pricca P. The use of indomethacin to treat acute rises of intracranial pressure and improve global cerebral perfusion in a child with head trauma. Acta Anaesthesiol Scand 1997;41:536-540.