Special review

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

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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). In one study, impaired vasoactivity to hyperventilation in combination with a raised ICP correlated with a poor outcome with a mortality/vegetative state/severe disability rate of almost 100%. Recent estimates have shown that 70 - 80% of patients with severe head injuries have intracranial hypertension, 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. 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 intracranial

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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 hypoxia 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.11

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 (CMRO2) 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 PaCO2) 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 autoregulation2,7 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 albumin49 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).59

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 hypoaldosteronism 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-
The effect of indomethacin on intracranial pressure

a) Cerebral blood flow

In TBI an increase in CBF is associated with an increase in ICP, although initially (for the first few hours at least), cerebral blood flow decreases. Thereafter, CBF increases and may lead to intracranial hypertension and sometimes "malignant brain oedema." Studies have demonstrated a decrease in CBF following administration of indomethacin in the rat, gerbil, rabbit, cat, dog, goat, primate, pig and normal humans.

In controlled studies on human volunteers, 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.

Table 1. Cerebral blood flow change with indomethacin administration

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient</th>
<th>CBF (mL/100g/min)</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pickles et al</td>
<td>6</td>
<td>81.6 → 60.7</td>
<td>25</td>
</tr>
<tr>
<td>Therkelsen et al</td>
<td>29</td>
<td>(60 - 62) → (39 - 40)</td>
<td>33 - 37</td>
</tr>
<tr>
<td>Jensen et al</td>
<td>60</td>
<td>(65 - 68) → (44 - 48)</td>
<td>26 - 35</td>
</tr>
<tr>
<td>Jensen et al</td>
<td>29</td>
<td>(45 - 80) → (24 - 57)</td>
<td>33 - 40</td>
</tr>
</tbody>
</table>

CBF = cerebral blood flow

Recent trials indicate that patients with TBI and intracranial hypertension who have impaired CO2 reactivity have a poor prognosis, with conventional non-surgical therapies often being ineffective. In these patients indomethacin may be useful. 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 O2 saturation (i.e. > 60%) and/or a relatively high CBF (i.e. > 40mL/100g/min).

b) Cerebrospinal fluid production

Shalk et al 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, and the brain is very sensitive to temperature changes during periods of raised ICP and ischaemia. Indomethacin may therefore be neuroprotective by lowering cerebral temperature and therefore ICP by preventing hyperpyrexia.

Clinical studies of indomethacin in traumatic brain injury

Post traumatic brain oedema is common 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.

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" using β antagonists, α2 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, compared with 100% mortality in a group of patients treated by conventional therapy in identical entry criteria controls. Indomethacin, as a cerebral precapillary vasoconstrictor, has also been studied in patients with head injury.

Jensen et al 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 PaCO2 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 CMRO₂ 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 subarachnoid 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 ± 11.4 mg/hr over 30 ± 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 PaCO₂ 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 AVDO₂ using indomethacin in 9 patients having craniotomy for supratentorial cerebral

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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>No.</th>
<th>Treatment</th>
<th>∆ICP</th>
<th>∆CPP</th>
<th>∆CBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen, et al.¹⁰⁰</td>
<td>Case series</td>
<td>5</td>
<td>30mg iv then 30mg/hr for 7 hr</td>
<td>28 → 17 (p &lt; 0.05)</td>
<td>67.0 → 76.4 (p &lt; 0.05)</td>
<td>34 → 25 (p &lt; 0.05)</td>
</tr>
<tr>
<td>Biestro, et al.¹⁰⁷</td>
<td>Case series</td>
<td>10</td>
<td>50mg i.v infusion 30 hr</td>
<td>34.4 → 16.4 (p &lt; 0.05)</td>
<td>73.8 → 81.0 (p = 0.001)</td>
<td>39 → 30 (p = 0.001)</td>
</tr>
<tr>
<td>Dahl, et al.¹⁰⁸</td>
<td>P.Obs</td>
<td>14</td>
<td>30mg bolus</td>
<td>15.0 → 9.4 (p &lt; 0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clemmensen, et al.¹⁰⁹</td>
<td>Case report</td>
<td>1</td>
<td>25mg i.v boluses</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hansen, et al.¹¹⁰</td>
<td>Case report</td>
<td>1</td>
<td>30mg i.v boluses</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bungaard, et al.¹¹¹</td>
<td>Case series</td>
<td>9</td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imberti, et al.¹¹²</td>
<td>Case report</td>
<td>1</td>
<td>5-10mg i.v boluses</td>
<td>68.0 → 22.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSION

Indomethacin is a pharmacological alternative for the management of refractory ICP elevation in severe head injury.\textsuperscript{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.\textsuperscript{31,40,107,110,112}

However, concerns relating to indomethacin induced cerebral ischaemia caused by reducing CBF are real. Both Jensen \textit{et al}.\textsuperscript{40} and Dahl \textit{et al}.\textsuperscript{108} demonstrated CBF < 20 mL/100g/min with $\text{SjV\textsubscript{O\textsubscript{2}}}$ < 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 $\text{SjV\textsubscript{O\textsubscript{2}}}$ (> 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.

Received: 16 August 2002
Accepted: 10 October 2002

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