



Side Effects of Indomethacin in Refractory Post-traumatic Intracranial Hypertension: A Comprehensive Case Study and Review

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ABSTRACT

Intracranial hypertension (IH) is one of the final pathways of acute brain injury. In severe traumatic brain injury (sTBI), it independently predicts poor outcomes. Its control represents a key aspect of the management. Lack of response to conventional therapies signals a state of "refractory IH", with an associated mortality rate of 80-100%. In such cases, hypothermia, barbiturates at high doses (BBT), decompressive craniectomy (DC), and extreme hyperventilation are utilized. However, none of them has proven efficacy. Indomethacin (INDO), a non-steroidal anti-inflammatory drug, may be an option with an acceptable safety profile and easy to administer. Reported series showed encouraging results. We herein present a case of refractory IH after sTBI in which INDO was utilized. In refractory IH, INDO can help to decrease ICP and improve cerebral perfusion pressure. However, it requires administration under strict protocol since it's not free of adverse effects after withdrawal.

Keywords: Indomethacin; Traumatic brain injury (TBI); Refractory intracranial hypertension; Cerebral blood flow; Rebound effect; Side effects.

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Introduction

Intracranial hypertension (IH) is one of the most frequent causes of death after severe traumatic brain injury (sTBI), especially when it is not responsive to conventional therapy [1-3]. The lack

of response to first-line therapy signals a state of "refractory IH", which has a prevalence of 15% and very high mortality, ranging between 80% and 100% [1-3]. In this situation, treatment options are limited and to date, they did not demonstrate impressive efficacy [4-6].

Indomethacin (INDO) is a non-steroidal anti-inflammatory agent with cerebral vasoactive properties [7-10]. Its administration decreases ICP due to an immediate and dramatic reduction in cerebral blood flow (CBF) [7-10]. This phenomenon occurs without significant alteration in the metabolic rate of oxygen (CMRO₂) or glucose [11-14]. Despite vasoconstriction after INDO administration, brain ischemia has not been convincingly demonstrated [11-15]. Additionally, INDO has other potential benefits. It can modulate the autoregulatory capacity of the cerebral vasculature, decrease cerebrospinal fluid (CSF) production, and prevent edema formation [16-19]. Moreover, INDO has neuroprotective properties via inhibition of neurotoxic products derived from the metabolism of arachidonic acid [7-10]. Some clinical series showed that INDO may be an alternative therapeutic option in life-threatening refractory IH [20-25]. INDO has acceptable safety profile, is inexpensive and easy to administer. However, INDO needs to be withdrawal slowly, because sudden cessation can provoke rebound elevations in ICP [7-10, 20-24].

Case Report

A 33-year-old man, Jehovah’s Witness without medical history, was involved in a motorcycle accident. He was found at 45 meters from the collision site in coma with motor response in decortication) to pain. Glasgow Coma Scale (GCS) was 5: (O₁), (V₁), (M₃). Both pupils showed size, shape, and reactivity

normal. Hypoxemia (pulse oximetry = 83%) and arterial hypotension (blood pressure 70/40 mmHg) was detected at scene. ABC (airway, breathing, circulation) of resuscitation was immediately started with fluids (normal saline), endotracheal intubation, assisted ventilation, oxygenation and cervical spine immobilization. At emergency department, GCS did not change after adequate and complete resuscitation. After clinical stabilization, the patient was transferred to the radiology department. Computed tomography (CT) scan showed effacement of basal cisterns, diffuse traumatic subarachnoid hemorrhage, right frontal contusions <25 cc and acute fronto-temporal subdural hematoma. Three-dimensional reconstruction showed a long-line fracture that crosses all frontal bone extended to the contralateral occipital bone. Figure 1A CT scans of the cervical spine, thorax and abdomen not showed alterations. Closed fracture of left tibia and peroneus, were stabilized with skeletal traction.

Neurosurgeon decided hematoma evacuation and right decompressive hemicraniectomy with enlarged duroplasty. An intraparenchymal pressure monitor (Codman Micro sensor

Basic Kit bolt) was inserted at Kocher’s point on the right side via twist drill craniostomy. Initial ICP was 47 mmHg; decreased to 28 mmHg after removal of the bone flap, stabilizing in 12 mmHg after dura matter opening. After the procedure, the patient was admitted to the intensive care unit (ICU) mechanically ventilated, under sedation and analgesia (Richmond Agitation Sedation Scale: -5),

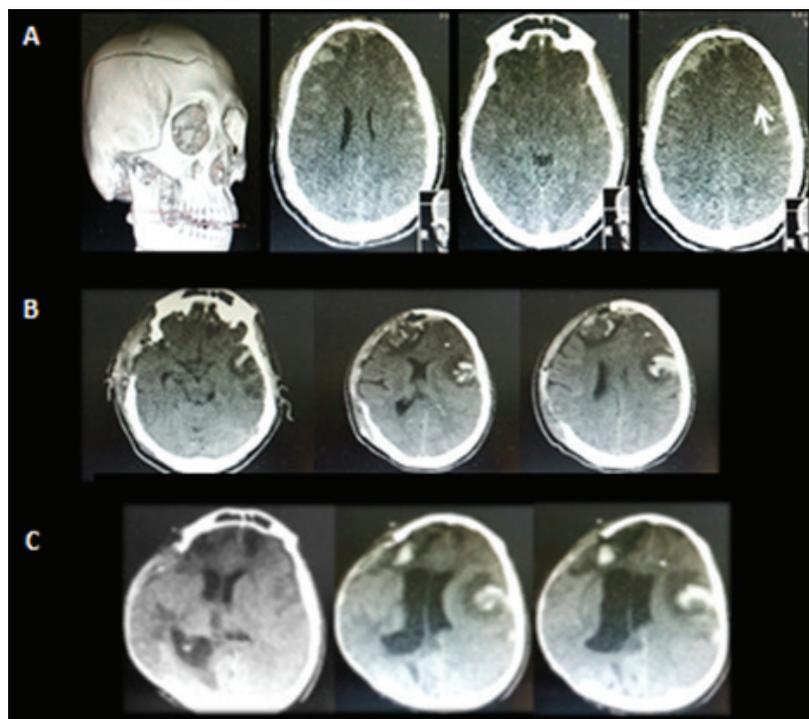


Fig. 1 A. CT scan at admission; **1B.** CT scan after initial surgery; **1C.** CT scan during clinical worsening and rebound increase of ICP (intracranial pressure).

3D view showed long-line fracture crossing all frontal bone extended to the contralateral occipital bone; traumatic subarachnoid hemorrhage; right frontal contusion; effacement of sulcus and basal cisterns; and acute subdural hematoma (arrow).

Decompressive craniectomy. Open basal cisterns, increase volume of right frontal contusion and a new left temporal contusion(left to right midline shift of 5 mm).

with miotics and reactive pupils. Vital parameters were: mean arterial pressure (MAP) 92 mmHg, Heart Rate 76 beats/min; central temperature 35.7 °C (esophagus) and respiratory rate 16 breaths/min, ICP and cerebral perfusion pressure (CPP) were 8 and 84 mmHg respectively. Laboratory parameters at ICU admission are reported in Table 1.

The first two days, ICP remained stable below 15 mmHg with general measures: sedation, analgesia, mechanical ventilation, neutral head position at 30 degrees of the horizontal. Secondary insults were rigorously avoided maintaining normal basic physiological parameters: paCO₂ between 35-40 mmHg, PaO₂ > 90 mmHg, normothermia (central temperature <37.5°C), normovolemia (CVP 10-12 mmHg with diameter of inferior cava vein between 1.5-2 cm), ensuring a slightly salty (Serum sodium between 145-155 mEq/L and sweaty (Glycaemia levels between 110-180 mg/dL) microenvironment. CPP was maintained (without inotropic or vasopressors) between 60-70 mmHg.

At 3rd day from admission, ICP dramatically increased. Secondary insults as cause of ICP increase were discharged and MABP was stable. A new CT showed increased volume of right frontal contusion and a new left temporal contusion with left to right midline shift of 5 mm (Figure 1B).

Both contusions were not evacuated for neurosurgeon decision and conservative management was decided by the refusal of the family to authorize surgery. Initially, IH was controlled with the addition of osmotherapy (mannitol at 15% and hypertonic

saline at 7.5%) [24, 25]. At the end of 5th day, both solutions reached their utilization limits (serum sodium: 160 mEq/L) and osmolarity (322 mosm/L), and additionally non-response was observed after newer doses, so refractory IH was diagnosed. Mild hyperventilation was started (paCO₂: 30-35 mmHg) but non response to ICP values was observed with decrease of jugular bulb saturation (SvJO₂) values at < 50%. Barbiturates at high doses (tiopental) in continuous infusion were not utilized because of the lack of response of ICP values and severe arterial hypotension associated with loading dose. Mild hypothermia (34.5-35.5) was induced but shivering of difficult management and ventricular arrhythmias forced to change the strategy to controlled normothermia.

Intravenous INDO infusion was started at 0.5 mg/kg/h after a loading dose of 0.8 mg/kg [24, 25]. Immediately after INDO, ICP decreased to 14 mmHg and CPP increased to 73 mmHg and both parameters remained controlled during a 3 days period. Rectal temperature remained stable and within normal range during evolution (Figure 2).

At 9th day of evolution ICP increase again despite indo infusion and osmotherapy and all general measures of physiologic neuroprotection previously signaled. Sepsis, septic shock and multi-organ dysfunction syndrome developed.

Norepinephrine was necessary to maintain adequate MAP and CPP levels. Acute respiratory distress syndrome (ARDS) was diagnosed and urea and creatinine levels signaled acute renal dysfunction.

Table 1. Laboratory parameters at admission; 3th and 9th day of evolution.

Parameter	ICU admission	5th day	9 th day
pH	7.36	7.38	7.35
paCO ₂	34 mmHg	35 mmHg	33 mmHg
paO ₂	127 mmHg	132 mmHg	89 mmHg
HCO ₃ ⁻	22 mEq/L	22 mEq/L	14 mEq/L
Base Excess	-3	-2	-12
Na ^{+a}	132 mEq/L	145 mEq/L	159 mEq/L
K ^{+b}	3.8 mEq/L	3.6 mEq/L	4.6
Cl ^{-c}	107 mEq/L	108 mEq/L	114 mEq/L
Lactate	2,2 mmol/L	1.8 mmol/L	18.5 mmol/L
Blood glucose	117 mg/dL	105 mg/dL	125 mg/dL
Blood urea	0.25 g/dL	0.32 g/dL	0.97 g/dL
Creatinine	0.9 mg/dL	1 mg/dL	3.6 mg/dL
WBC ^d	11.700/mm ³	13.600/mm ³	21.900/mm ³
Hemoglobin	10.3 g/dL	9.2 g/dL	6.5 g/dL
ALP ^e	87 U/L	88 U/L	96 U/L
ALT ^f	44 U/L	52 U/L	65 U/L
AST ^g	36 U/L	44 U/L	67 U/L
Albumin	3.1 g/dL	2.6 g/dL	2.2 g/dL
Total bilirubin	0.8 mg/dL	1.1 mg/dL	1.4 mg/dL
Prothrombin concentration	75%	59%	36%
aPTT ^h	29 seconds	28 seconds	115 seconds
Platelets count	227.000/mm ³	197.000/mm ³	37.500/mm ³
Fibrinogen	312 mg/dL	223 mg/dL	52 mg/dL

^aNa⁺: serum sodium; ^bK⁺: serum potassium; ^cCl⁻: serum chloride; ^dWBC: white blood count; ^eALP: alkaline phosphatase; ^fALT: alanine aminotransferase; ^gAST: aspartate aminotransferase; ^haPTT: activated partial thromboplastin time

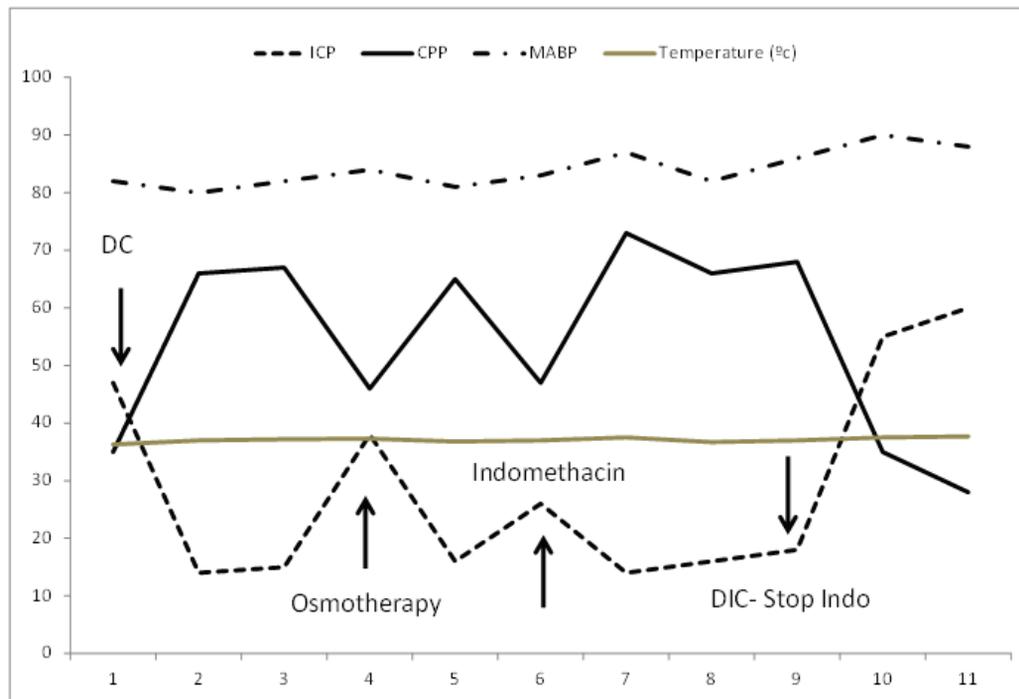


Fig. 2. Temporal profile of MABP; ICP; CPP and rectal temperature (°C) in the reported case.

DC: decompressive craniectomy; MABP: mean arterial blood pressure; ICP: intracranial pressure; CPP: cerebral perfusion pressure; INDO: indomethacin; DIC: disseminated intravascular coagulation.

Bleeding gums, hematuria and hematemesis with a marked decrease in hemoglobin level to 6.5 gr/dL were present. Blood cultures and broncho alveolar lavage were positive for *Acinetobacter baumani*. Coagulation parameters signaled Disseminated Intravascular Coagulation (DIC): prothrombin concentration (PT) 36%, partial thromboplastin time (APTT) 115 seconds, fibrinogen 52 mg/dL, and platelets count 37500/mm³ (Table 1).

Due to DIC, thrombocytopenia and renal dysfunction, INDO was slowly withdrawal (Figure 3). Intravenous K vitamin and 4 coagulation factors concentrate were started.

Platelets, blood, plasma or cryoprecipitates, were not administered due to negative of the family and legal representative by religious convictions.

During INDO withdrawal, ICP increase to 64 mmHg and nonreactive right mydriasis was present. New CT scan did not showed any new bleeding, enlargement of pre-existing collections, or evidence of infarction, however, an increase of cerebral edema with marked midline shift (displacement vector from left to right) with subfalcine and uncal herniation was observed (Figure 1C).

Hypothermia and BBT were contraindicated due to septic shock and severe myocardial depression (ejection fraction < 30%) and non-response to osmotherapy was observed after repeated doses. The patient was transferred to surgical room. Left DC and ventriculostomy was performed, but ICP levels not decrease. 2 Hours after surgery, the patient developed fixed bilateral pupils with severe hemodynamic instability, and 12 hours later he died.

Discussion

Indomethacin for Intracranial Hypertension Control (IH)

IH is a recognized cause of death in patients with STBI, especially when cannot be controlled with conventional therapies [1-3]. In these ‘refractory’, circumstances, there are not standardized or widely validated treatments [4-6]. Options include barbiturates at high (BBT) doses, hypothermia, profound hyperventilation or decompressive craniectomy (DC). However, all are associated with severe and life threatening side effects and none of them have proven efficacy [2, 4-6, 26-31]. Despite DC and conventional therapies, our patient developed refractory IH. During INDO infusion, ICP decrease and CPP increase. These results are consistent with previous studies [20-25]. The early and profound responses of ICP and CPP to INDO suggest that the primary effect of this drug is related to its vasoactive properties [7-10]. Multiple experimental and clinical studies have confirmed that INDO reduces CBF possibly via attenuation of prostaglandin synthesis [8, 9, 14, 21, 32-37]. Prostaglandins play a significant role in regulation and modulation of vascular tone and CBF [38]. Neuroprotection, positive effects on cerebral autoregulation and antipyretic are other beneficial properties attributed to INDO [7-10, 20]. A recent systematic review concluded that INDO decrease ICP without significant complications. Current evidence signaled GRADE C. Oxford level 2b to support INDO utilization for ICP control after severe TBI [39].

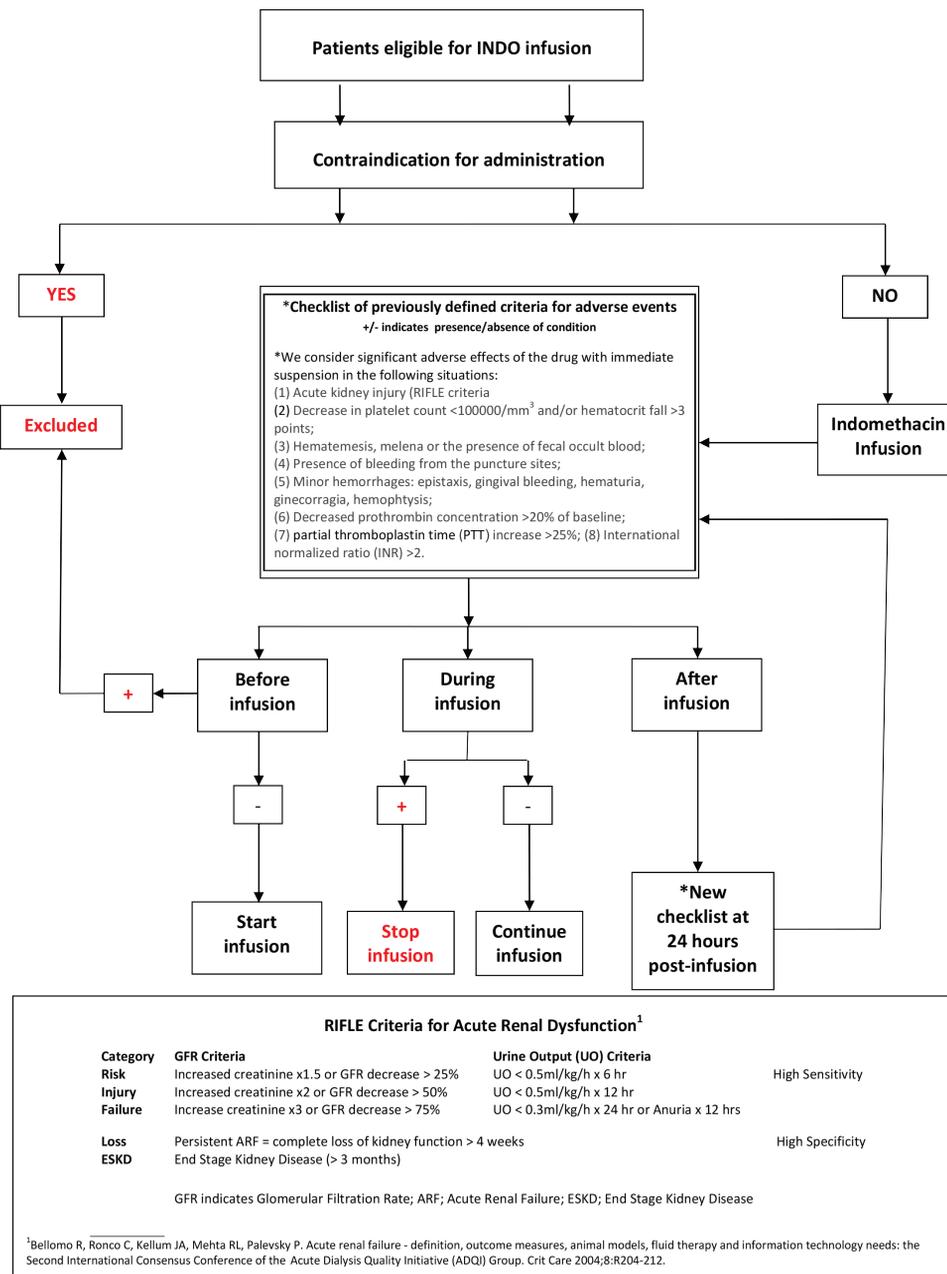


Fig. 3. Protocol for control of adverse events during INDO infusion.

Indomethacin and Side Effects

The major side effects associated with INDO are gastrointestinal bleeding, disorders of coagulation, acute renal injury, cerebral ischemia and rebound intracranial hypertension after withdrawal of the drug.

Coagulation Alterations

Different degrees and types of coagulopathy have been described after sTBI [40-42]. Hypercoagulable states predispose to ischemia whereas hypocoagulable states predispose to bleeding [40-42]. Its real significance has not been elucidated yet, but coagulations disorders are known factors of secondary injury [40-42]. INDO has antiplatelet properties through reversible and short duration inhibition of cyclooxygenase [7-10, 14, 43, 44]. More than 40% of platelet function recovery 24 hours after

stop INDO infusion [38]. INDO increases bleeding time without clinical consequences [44-48]. The reported incidence of minor bleeding during INDO infusion in the postoperative period of orthopedic surgery was 14.3% [46], however, when INDO was employed to control IH in severe TBI or fulminant hepatic failure, bleeding complications never were reported [16,21-25,49] (Table 2).

From a pathophysiological point of view, sepsis is an uncontrolled inflammatory and pro-coagulant response to infection. Platelets play a key role, via interaction with endothelial cells, coagulation and immune systems [50-52]. In this context, the antiplatelet effect of indo could be beneficial. Some data suggest a protective effect of antiplatelets in sepsis and in the development of DIC [51-52]. Moreover, as far as we know, DIC as a complication

Table 2. Reported adverse effects of Indomethacin when it was utilized for control of intracranial hypertension.

Author	Year	Population	n ^a	Doses	Time period	Adverse Effects			
						Cardiac	Renal	Gastrointestinal	Coagulopathy
Jensen [21]	1991	TBI ^c	5	30 mg (load) 30 mg/kg/h (infusion)	7 h	NR ^b	NR ^b	NR ^b	NR ^b
Biestro [20]	1995	TBI ^c SAH ^d	10 1	50 mg (load) 21.5±11/h (infusion)	30±9 h	NR ^b	NR ^b	NR ^b	NR ^b
Hansen [59]	1995	AVM ^e	1	30 mg (bolus)		NR ^b	NR ^b	NR ^b	NR ^b
De Deyne [60]	1995	TBI ^c	6	NR ^b	NR ^b	NR ^b	NR ^b	Gut infarction (1)	NR ^b
Imberti [61]	1997	TBI ^c	1	5-10 mg (bolus)	18 occasions	NR ^b	NR ^b	NR ^b	NR ^b
Clemmesen [23]	1997	FHF ^f	1	25 mg (bolus)	4 occasions	NO	YES (previous)-HD	NO	NO
Schwarz [62]	1999	MMCAI ^g	1	50 mg (bolus) 30 mg/h (infusion)	NR ^b	NR ^b	NR ^b	NR ^b	NR ^b
Bewley [63]	2000	TBI ^c	10	3-11 mg/h (infusion)	3.8 days	NO	YES (2) Septic shock	NO	NR
Forderreuter [64]	2000	IIH ^h	7	50 mg (bolus)	1 occasion	NO	NO	NO	NO
Tofteng [48]	2004	FHF ^f	12	25 mg (bolus)	1 occasion	NO	NO	NO	NO
Imberti [22]	2005	TBI ^c ICH	7 2	15-20 mg (bolus)	NR ^b	NR ^b	NR ^b	NR ^b	NR ^b
Puppo [16]	2007	TBI ^c	16	0.6-0.8 mg/kg (load) 0.3-0.5 mg/kg/h (infusion)	NR ^b	NR ^b	NR ^b	NR ^b	NR ^b
Godoy [24]	2012	TBI ^c ICH ⁱ	10 13	0.8 mg/kg (load) 0,5 mg/kg/h (infusion)	35±8 h	NO	NO	NO	NO
Godoy [25]	2014	TBI ^c	32	0.8 mg/kg (load) 0,5 mg/kg/h (infusion)	32 h	NO	NO	NO	NO

^an: number of patients; ^bNR: not reported; ^cTBI: traumatic brain injury; ^dSAH: subarachnoid hemorrhage; ^eAVM: arteriovenous malformation; ^fFHF: fulminant hepatic failure; ^gMMCAI: malignant middle cerebral artery infarction; ^hIIH: idiopathic intracranial hypertension (pseudo tumor cerebri); ⁱICH: spontaneous intracerebral hemorrhage

of INDO never was signaled [7-10, 16, 21-25, 26, 44-49]. While we cannot rule out completely INDO contribution to coagulopathy and symptomatic bleeding; there were no clinical signs of hemorrhage and laboratory parameters remained normal during period of infusion of INDO. Moreover, follow-up CT scans not showed new o progressive bleeding.

Renal Injury

Different pattern of renal compromise were described after non-steroidal anti-inflammatory drugs (NSAIDs) utilization principally when prostaglandin synthesis is blocked [53]. INDO, by interfering with prostaglandin pathway, can lead to acute renal damage, especially when volume contraction or hemodynamic instability was present [54]. Acute interstitial nephritis is other mechanism of injury [53, 55]. A recent meta-analysis confirmed the risk of acute kidney injury when NSAIDs are used. The risk is similar regardless of the drug used.

These side effects have close association with doses and duration of treatment [55]. In our clinical case, we don't discharge completely INDO contribution to renal injury, however, hypovolemia was rigorously avoided, the doses utilized there were below the range of toxicity and the infusion period was brief.

Cerebral Ischemia and Rebound Intracranial Hypertension

Despite CBF reduction due to cerebral vasoconstriction INDO does not compromise oxygen cerebral consumption (CMRO₂) maintaining proper metabolic-vascular coupling [11-14]. Functional magnetic resonance and positron emission tomography (PET) studies have evidenced that INDO do not cause cerebral ischemia possibly due to maintain a good reserve capacity to extract oxygen [11-14]. Rebound ICP elevation is a signaled complication after abrupt cessation of INDO due to abrupt vasodilatation and increase of cerebral

blood volume [7-10]. To avoid this phenomenon, the withdrawal of the drug should be slowly as the reported case (25% doses every 6 hours) [24, 25]. Whereas this complication was signaled in literature, never was reported.

Limitations

The reported case has limitations. First, we do not monitor cerebral oxygenation parameters (jugular bulb oximetry or brain tissue oxygen pressure) continuously, whereby episodes of tissue hypoxia secondary to vasoconstriction during INDO infusion could be unnoticed. Second, while follow-up CT scans did not show ischemic complications, we recognize the limitations of this technique to detect brain ischemia. Third, conventional coagulation parameters do not always detect all aspect of coagulation disorders in trauma or sepsis, so it's impossible to us to establish with certainty the relationship between indo and coagulation alterations reported. Finally, since adverse effects were not the focus of previous INDO studies, we cannot rule out that complications secondary to the drug were underreported.

In conclusion, the case reported is complex. Our patient developed DIC and renal compromise

associated with sepsis and multi-organ dysfunction syndrome caused by multiresistant *Acinetobacter baumani*. DIC and renal dysfunction forced INDO withdrawal. Previous to stop INDO infusion, ICP begins to increase and more later became refractory. While the suspension of INDO may contribute to raise ICP, is not the only reason, since multiple factors of secondary injury (inflammation, blood brain barrier permeability increase, and edema) due to sepsis were present [56-58]. Moreover, the vector of displacement of the brain parenchyma is directed toward initial decompressive craniectomy, contralateral to consolidated hemorrhagic contusion which exerts its mass effect predominantly by inflammation and peri-contusional edema. Apparently, these mechanisms contribute to a delayed increase in ICP [56-58] (Figure 1C). Whereas in the reported case, the withdrawal of INDO was slowly, the causes of refractory intracranial hypertension and rebound increase of ICP were multifactorial. Finally application of indomethacin to treat intracranial hypertension shows promising result but more investigation is needed to shed light on all effects of this drug.

Conflicts of Interest: None declared.

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