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Perioperative Management of Traumatic Brain Injury

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Abstract

Purpose of Review Traumatic brain injury (TBI) is a global public health problem. It is increasingly being recognized as a progressive disease in which intrinsic pathophysiologic processes and systemic secondary insults aggravate the primary brain damage. The perioperative period is crucial in the continuum of the management of TBI. This review summarizes current anesthetic strategies to optimize TBI outcomes.

Recent Findings Perioperative data on TBI management are limited. However, recent findings indicate that intraoperative secondary insults are common and are associated with worse outcomes after intracranial as well as extracranial surgery in patients with TBI. The choice of anesthetic agents has not been shown to impact that the neurologic outcomes are TBI.

Summary Perioperative therapeutic goals for patients with TBI include facilitating early cerebral decompression, providing balanced anesthesia for surgery, maintaining adequate cerebral perfusion by optimizing systemic and intracranial hemodynamics, and aggressively avoiding secondary insults. Intensive multimodal monitoring of the brain provides vital information that may be helpful in individualizing therapy; such monitoring should be continued in the perioperative period, particularly during extracranial surgery in TBI patients with polytrauma. While further investigation to characterize the impact of anesthetic agents on the injured brain and their effect on clinical outcomes is awaited, perioperative management should focus on adherence to consensus guidelines.

Keywords Traumatic brain injury · Anesthesia · Perioperative · Secondary insult

Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide [1]. Anesthesiologists are involved in the care of patients with TBI in various situations including resuscitation and stabilization in the emergency department, providing anesthesia for evacuation of intracranial hematoma/decompressive craniectomy/ extracranial surgery, and during management on the intensive care unit (ICU). This review will focus primarily on the immediate perioperative management of adult patients with TBI undergoing surgery. While a uniform approach to treating TBI victims throughout the continuum of care appears intuitive, there are challenges that are unique to the various patient care locations. Irrespective, the overall goal of the perioperative management of TBI is to minimize further brain damage, prevent secondary insults, and institute potential neuroprotective interventions. The anesthetic plan should be individualized and cogent with overall treatment goals.

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Pathophysiology of TBI

The pathology of TBI involves a primary injury that occurs at the time of the trauma and secondary injury caused by subsequent alteration of homeostasis. The initial direct trauma causes mechanical distortion, stretch and disruption of cerebral tissue resulting in focal or global alterations in cerebral autoregulation, blood flow (CBF), and metabolism [2–4]. Secondary insults such as hypotension and hypoperfusion cause further brain damage and contribute to worse outcomes [5, 6]. Brain trauma can be viewed as an acute cerebral energy crisis followed by a chronic energy shortage. The initial injury causes a release of glutamate that activates N-methyl-D aspartate receptors causing cellular efflux of potassium and influx of sodium and calcium. The adenosine triphosphate (ATP)ase pump quickly consumes ATP, depleting cells of energy in the setting of disruption of supply of oxygen and metabolic substrate [7]. A reactive global increase of cerebral glucose uptake is followed by a decrease in glucose uptake, particularly in the penumbral area surrounding the initial injury [8, 9]. The depletion of ATP and energy results in an increase in the production of free radicals and decrease in the antioxidant capacity of cells. Under normal circumstances, mitochondria transport electrons across the transport chain, but this mechanism breaks down following injury leading to a cellular energy crisis. The mitochondria are also unable to handle excess calcium and activate multiple enzymes capable of producing more free radicals [10].

The vascular derangement in TBI is a consequence of shearing and mechanical forces causing local or global abnormalities. Damage to the endothelial lining of cerebral vessels, decreased amounts of nitric oxide and cholinergic neurotransmitters, and an increase of prostaglandin induce vasoconstriction leading to decreased CBF and ischemia. Reduced CBF following TBI can result in focal or regional ischemia, which can be a portent of poor outcome [11, 12]. The key to prevention/ avoidance of a cerebral ischemic cascade leading to worsening brain damage is the maintenance of adequate CBF. Consequently, cerebral hypoperfusion and hypoxia should be aggressively avoided in the perioperative period to minimize secondary brain damage.

Perioperative Management of TBI

Instead of being considered an isolated traumatic event, TBI is increasingly recognized as a progressive disease in which intrinsic pathophysiologic processes and systemic secondary insults aggravate the primary brain damage. It is now well accepted that the initial injury may evolve into a chronic disease. Consequently, the perioperative period is crucial in the continuum of the management of TBI. While surgery and anesthesia may predispose patients to new onset secondary injuries which may contribute adversely to outcomes, the perioperative period is also an opportunity to detect and correct undiagnosed pre-existing secondary insults and to prevent new insults [13]. The clinical management of TBI is largely guided by the recommendations of the Brain Trauma Foundation, which are summarized in Table 1 [14]. Adherence to guidelines in the perioperative period has been shown to be associated with decreased mortality and improved outcomes [15••, 16]. Despite the fact that these guidelines are evidence-based and have substantially improved the standards of TBI care, they do not account for the heterogeneity of TBI. In fact, it appears that guidelines have facilitated uncritical adoption of standardized approaches to TBI management without accounting for individual variation. While the adoption of guidelines is expected to reduce mortality overall, further improvement in functional outcome will likely require identification of targets for precision medicine and individualized care. Neuroimaging and biomarkers will likely contribute to better phenotyping and the development of more precise (individualized) treatment strategies. For perioperative TBI management, this might have implications in terms of individualized physiological/biochemical targets as well as administration of potential neuroprotective therapies. Meanwhile, current management of TBI emphasizes the following [14]:

- Targeted management of cerebral perfusion pressure (CPP), mean arterial blood pressure (MAP), and intracranial pressure (ICP);
- Maintenance of normoglycemia, normothermia, and oxygenation;
- Prevention of secondary injury and supporting overall recovery from concomitant extracranial injuries.

Anesthetic Agents for Traumatic Brain Injury

The intravenous and inhaled anesthetic agents differ significantly in their effects on cerebral physiology. In general, volatile anesthetic agents cause a dose-dependent uncoupling of CBF and cerebral metabolic rate for oxygen (CMRO$_2$) leading to cerebral vasodilation and increased ICP [17–20]. At concentrations <1.0 MAC, the cerebral vasodilatory effects of inhaled anesthetics are minimal, and their vasodilating effects can also be blunted by increases in minute ventilation. The intravenous agents, including thiopental, propofol, and etomidate, cause cerebral vasoconstriction and reduce cerebral blood volume (CBV) and ICP, while preserving the coupling of CBF and CMRO$_2$

Table 1 Guideline recommendations for the management of severe Traumatic Brain Injury [14]

Physiological parameters	Guideline recommendations
Blood Pressure	Monitor and avoid hypotension (SBP <90 mmHg) (level II recommendation)
Oxygenation	Monitor and avoid hypoxia (PaO_2 <60 mmHg or SPO_2 <90 %) (level III recommendation)
ICP	ICP should be monitored in patients with severe TBI and abnormal CT scan (level II recommendation) and in patients with normal CT scan if two or more of the following are present: age >40 years, motor posturing, systolic blood pressure <90 mmHg (level III recommendation)
	Treatment should be initiated if ICP >20 mmHg (level II)
CPP	Avoid aggressive treatment with fluids and pressors to maintain CPP > 70 mmHg because of the risk of ARDS (level II recommendation)
	CPP <50 mmHg should be avoided (level III recommendation)
Hyperventilation	Prophylactic ventilation ($PaCO_2$ ≤25 mmHg) is not recommended (level II recommendation)
	Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP (level III recommendation)
Hyperosmolar therapy	Mannitol (0.25–1.0 g/kg) is effective for control of raised ICP. However, hypotension with Mannitol should be avoided (level II recommendation)
	Restrict Mannitol use prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurological deterioration not attributable to extracranial causes (level III recommendation)
Steroids	In patients with moderate or severe TBI, high-dose methylprednisolone is associated with increased mortality and is contraindicated (level I recommendation)
Temperature	Prophylactic hypothermia is not significantly associated with decreased mortality (level III recommendation)
	Hypothermia may have a higher chance of reducing mortality when cooling is maintained for more than 48 h (level III recommendation)
Cerebral oxygenation	Treat when jugular venous saturation is <50 % or brain tissue oxygen tension is <15 mmHg (level III recommendation)

TBI Traumatic brain injury, *SBP* Systolic blood pressure, *ICP* Intracranial pressure, *CT* computed tomography, *CPP* Cerebral perfusion pressure, *ARDS* adult respiratory distress syndrome

[19–23]. However, the electroencephalographic burst-suppression induced by propofol after TBI does not significantly change brain tissue oxygen levels, tissue chemistry, or arterial–jugular venous oxygen differences and does not appear to reduce the regional ischemic burden [24]. While cerebrovascular pressure autoregulation is preserved with propofol infusion in healthy individuals, high-dose propofol (plasma target concentration of ∼4.3 mcg/mL) may worsen static cerebral autoregulation in patients with TBI thereby increasing vulnerability to secondary insults [25].

Importantly, the choice of anesthetic agents (inhalation vs. Intravenous) has not been shown to impact outcomes after TBI. A retrospective study did not find an association between type of anesthetic agent, i.e., intravenous or inhaled, and neurologic outcome [26]. Half the patients who received intravenous anesthesia in this series received ketamine, and there was also no difference in outcome among these patients. In the absence of conclusive evidence, either inhaled or intravenous anesthesia may be employed judiciously after TBI. A balanced anesthetic technique, including analgesics and neuromuscular blocking agents, is the best, and the principles of anesthetic management should adhere to the current guidelines for the management of severe TBI [14].

Perioperative Monitoring

In additional to standard American Society of Anesthesiology (ASA) monitoring (electrocardiography, noninvasive blood pressure, pulse oximetry, capnography, and temperature), arterial catheterization is recommended to allow beat-to-beat blood pressure, arterial blood gas, and blood glucose monitoring. ICP monitoring is recommended in patients with a severe TBI and abnormal CT scan (hematomas, contusions, swelling, herniation, or compressed basal cistern), and in patients with severe TBI and a normal CT scan if two or more of the following are present: age >40 years, motor posturing, or systolic blood pressure <90 mmHg [14]. It is generally recommended that ICP should be maintained <20 mmHg and CPP 50–70 mmHg [14]. However, the role of ICP monitoring in improving neurological outcomes has recently been questioned. A randomized controlled trial assigning severe TBI patients to therapy directed either by ICP monitoring or clinical examination and imaging reported no difference in the primary outcome of a composite of survival time, impaired consciousness, and functional status at 3 and 6 months between these groups [27]. A subsequent systematic review and meta-analysis concluded that current clinical evidence

indicates that ICP monitoring-guided treatment of TBI has no mortality benefit compared to treatment in the absence of ICP monitoring [28]. Recent guidance recommends that there is no indication for ICP monitoring in comatose TBI patients with a normal computed tomography (CT) scan, but that ICP monitoring should be undertaken in comatose TBI patients with cerebral contusions in whom clinical examination cannot be performed due to sedation [29]. It remains widely accepted that ICP management has the potential to influence outcome, particularly when care is targeted, individualized, and supplemented with data from other monitors [30].

Monitoring cerebral oxygenation (global or focal), CBF or metabolic parameters may be helpful in guiding treatment decisions after TBI [16]. In TBI patients with polytrauma, all monitoring should be continued during extracranial surgery. Jugular venous oximetry has been used to detect intraoperative cerebral desaturation and guide anesthetic interventions, such as optimizing hyperventilation therapy, management of CPP, fluids and oxygenation, in order to optimize cerebral physiology [31–33]. Jugular venous saturation $\leq 55\%$ has been shown to be associated with poor neurological outcome and should be avoided [34]. Continuous brain tissue oxygen monitoring (PtiO2) reflects both oxygen delivery and consumption. The normal $PtiO_2$ ranges from 20 to 35 mmHg, and the ischemic threshold from 10 to 15 mmHg; and values below 10 mmHg are associated with poor outcomes after TBI [35, 36]. Low brain $PtiO_2$ can be normalized by several strategies aimed at increasing cerebral oxygen delivery. Increasing CPP can improve brain $PtiO_2$ when cerebral autoregulation is impaired and the baseline $PtiO_2$ is low [35]. $PtiO_2$-guided therapy has also been linked to improved patient outcomes [36], although there are no data demonstrating the utility of $PtiO_2$ monitoring during surgery and anesthesia for TBI.

Measurement of the CBF velocity using Transcranial Doppler (TCD) ultrasonography can provide real-time information about changes in the cerebral circulation. TCD has been used to assess CBF during extracranial surgery in TBI patients, and to examine cerebral autoregulation and guide management of systemic physiological parameters [37]. Efforts to use TCD to estimate the CPP noninvasively have not been successful.

Perioperative Hemodynamic Management

Most TBI patients present initially with a high sympathetic tone and hypertension as the first response to the trauma. This can be followed by hypotension due to shock, administration of medications to treat cerebral hypertension such as Mannitol, or medications given to facilitate

intubation and airway management. The recommendation of the Brain Trauma Foundation is to maintain systolic blood pressure >90 mmHg and avoid CPP <50 mmHg [14]. When presenting for emergent evacuation of intracranial hematoma, most patients do not have an ICP monitor in place, and reliance on systolic blood pressure to guide management ignores the main driving force behind CPP, i.e., the MAP. From a practical perspective, maintaining MAP >80 mmHg in a patient requiring acute cerebral decompression is likely to ensure CPP >50 mmHg. Hypotension during emergent craniotomy for TBI occurs in 32–65 % patients and may be associated with increased hospital mortality [38, 39]. The risk factors for intraoperative hypotension are low admission Glasgow Coma Scale (GCS) score, preoperative tachycardia and hypertension, the presence of a subdural hematoma (SDH) or multiple cranial CT lesions, maximum thickness of the CT lesion and longer duration of anesthesia [39]. Specifically, sudden decrease in blood pressure often occurs following removal of the bone flap and incision of the dura, which is thought to result from sudden loss of the Cushing's response [40]. This "decompression hypotension" may be predicted by low GCS score, the absence of mesencephalic cisterns on CT scan, and bilateral dilated pupils [40]. Intraoperative hypotension has recently been reported to occur in 60 % of TBI patients undergoing surgery for an associated orthopedic injury, and the resulting cerebral hypoperfusion was noted to lead to postoperative escalation of care [41••]. Essentially, intraoperative hypotension is common and potentially detrimental and, hence, must be avoided.

Normovolemia is the fluid resuscitation goal after TBI. In general, warm, nonglucose containing isotonic crystalloid solutions are preferable. Hypertonic saline solutions (HTS) increase intravascular volume while decreasing cerebral volume and ICP, and have other potential beneficial effects including relaxation of smooth muscle, liberation of prostacyclin from endothelial cells, vasodilation and liberation of endothelial relaxing factor [42–44]. In a post hoc analysis of trauma patients, those who received HTS in the prehospital period had higher blood pressures, decreased overall fluid requirements, and improved survival [45]. In the TBI subgroup of this study, statistically significant improvement at discharge was noted in those who received HTS. It remains to be elucidated whether the effects of HTS are due to improved MAP, innate systemic effects, or both. The controversy generated by the Saline versus Albumin Fluid Evaluation (SAFE) study [46], which demonstrated that resuscitation with albumin is associated with higher mortality rate and unfavorable neurological outcome at 24 months after TBI, still keeps many from using albumin, despite arguments refuting those findings. However, no guidelines currently recommend the use of

albumin after TBI [47]. The concerns about systemic adverse effects of starches and other colloids have also severely curtailed their use, and they too do not appear in any guidelines for the management of TBI.

Treatment with vasopressors to augment blood pressure can be instituted until normovolemia is achieved, or if adequate MAP cannot be maintained despite normovolemia. The choice of vasopressor to augment CPP in TBI remains controversial. In the United States, the pure alpha-adrenergic agent phenylephrine is used most frequently, followed by norepinephrine and dopamine [48]. While some studies demonstrate a superior increase in blood pressure with phenylephrine, at least one retrospective study points to improved cardiac function with norepinephrine that might result in beneficial outcome effects after TBI [49]. Since TBI-related cardiac dysfunction is common, the beneficial effects of norepinephrine on cardiac function lead some authorities to recommend that it should be the vasopressor of choice after TBI. Additionally, norepinephrine results in a more consistent increase in the CBF velocity and cerebrovascular resistance than dopamine [50]. In a study using positron emission tomography, $CMRO_2$ decreased when norepinephrine was used to increase CPP from 70 to 90 mmHg with [51]. One might extrapolate from this study that norepinephrine may increase CBF while decreasing consumption of oxygen, placing the traumatized area in a more favorable metabolic state. Anesthetic agents typically decrease systemic vascular resistance and MAP, so anesthesiologists should anticipate the need for vasopressors to augment blood pressure even in patients who arrive to the operating room without prior vasopressor need. The choice of vasopressor should take into account ICP, existence of cardiac dysfunction, coronary disease, and heart rate. Importantly, the arterial line should be zeroed at the level of the external auditory meatus (roughly at the level of the Circle of Willis), since accurate calculation of CPP requires that its components (MAP and ICP) are 'zeroed' at the same level.

Management of Intracranial Hypertension

The therapeutic options for reducing increased ICP include the following:

(a) *Adequate anesthesia, analgesia, and neuromuscular blockade*: Inadequate sedation/analgesia can potentially increase ICP due to the increased CBF associated with increased cerebral metabolic activity. Neuromuscular blockade prevents coughing or fighting the ventilator which can also increase ICP.

(b) *Positioning*: Careful positioning, including avoidance of obstruction to cerebral venous drainage by preventing excessive flexion and/or lateral rotation of the neck, is crucial.

(c) *Controlled ventilation, judicious use of hyperventilation, and maintenance of hemodynamic stability*: Prophylactic/prolonged and excessive hyperventilation may worsen cerebral ischemia and must be avoided.

(d) *Hyperosmolar therapy*: Both Mannitol and hypertonic saline are effective treatments of TBI-related intracranial hypertension. Mannitol (0.25–1.0 g/kg) reduces ICP by two distinct mechanisms—a reflex vasoconstriction caused by viscosity reduction leading to improved microvascular perfusion, and an osmotic diuretic effect. Hypertonic saline also has favorable rheologic and osmolar gradient effects but may offer other potential beneficial actions including restoration of normal cellular resting membrane potential and cell volume, inhibition of inflammation, and enhancement of cardiac output (see above).

(e) *Cerebrospinal fluid drainage*: An external ventricular drain (EVD) allows for a continuous monitoring of ICP and treatment of increases in ICP by allowing drainage of cerebral spinal fluid.

Glycemic Management

Hyperglycemia can cause secondary brain damage and has been shown to be associated with worse outcomes following TBI [52, 53]. However, tight glycemic control can increase cerebral metabolic crisis [53] and, interestingly, in vitro and in vivo studies suggest a direct benefit from increased glucose levels during the acute phase after TBI [54•, 55–57]. It is clear that glucose metabolism is disrupted in TBI and that the body tries to increase the availability of this important substrate. Hence, tight glucose control with intensive insulin therapy remains controversial, and may be undesirable in the intraoperative period when glucose values may fluctuate widely. Nevertheless, intraoperative hyperglycemia has been reported to occur in 15–20 % adults undergoing urgent/emergent craniotomy for TBI, and can be predicted by severe TBI, the presence of SDH, preoperative hyperglycemia, and aged ≥65 years [58, 59•]. Given the current evidence for glucose control for TBI in the perioperative period, a target glucose range of 80–140 mg/dl appears reasonable.

Hypothermia in TBI

Extensive research has explored the use of hypothermia as a therapeutic strategy to decrease ICP and improve neurological outcomes after TBI. Therapeutic cooling of the brain is postulated to attenuate secondary brain injury due

to amelioration of damaging inflammatory and neuroexcitatory cascades and elevated ICP [60–62]. Despite promising results in preclinical studies, the results of clinical studies are not encouraging and recent trials of hypothermia indicate a potential for clinical harm. The Eurotherm3235 Trial was a large randomized, controlled trial that tested therapeutic hypothermia as the primary intervention to reduce ICP after TBI when first-line ICP controlling therapies failed [63••]. In this trial involving patients with ICP >20 mm Hg for at least 5 min, despite first-line interventions (sedation, analgesia, mechanical ventilation, and head elevation), hypothermia plus standard care did not result in outcomes that were superior to those with standard care alone. Moreover, 36.5 % patients in the standard care group achieved a favorable outcome compared with 25.7 % in the hypothermia arm of the trial ($p = 0.03$), and the mortality in the hypothermia group was higher than that in the normothermia group (34.9 % vs. 26.6 %, hazard ratio, 1.45: 95 % CI 1.01–2.10; $p = 0.047$). The study was terminated early because of the adverse effects of hypothermia. In the perioperative period, particularly during anesthesia, patients are likely to become hypothermic but this is unlikely to provide any therapeutic benefit. In fact, hypothermia during acute bleeding may contribute to worsening coagulopathy and should be avoided.

Anesthesia for Extracranial Surgery

Patients with TBI often have associated other injuries which may require surgery, such as orthopedic, abdominal, and/or thoracic surgery. The timing and extent of the extracranial surgery depend on TBI severity as well as the severity of the extracranial injuries [64]. Importantly, the recovery of cerebral autoregulation after severe TBI can be delayed for weeks, particularly in patients with a lower GCS score, diffuse brain injury, and elevated ICP [65], and those with delayed recovery of autoregulation tend to have a worse outcome. Moreover, patients with traumatic subarachnoid hemorrhage are also at risk of cerebral vasospasm for 2–15 days after TBI, and this can exacerbate the risk of cerebral ischemia [66]. Consequently, the brain is susceptible to further ischemic damage even weeks after the original injury. Although hypotension should obviously be avoided during extracranial surgery after TBI, it has been reported in up to 60 % of adult cases and up to 78 % of pediatric cases [41, 67]. Not surprisingly, cerebral hypotension during extracranial surgery leads to escalation of postoperative care and lower chance of good neurological outcome. Other secondary insults, such as inadvertent hypercarbia and hypocarbia, are also common during extracranial surgery and potentially detrimental [41, 67].

The principles of anesthetic management of patients with TBI presenting for noncranial surgery are largely the same as those for craniotomy. Importantly, all preoperative monitoring should be continued during transport to the operating room and during surgery. In patients receiving antiepileptic medications, drug levels should be checked and administration continued uninterrupted perioperatively since seizures can increase ICP and cause further metabolic derangement [68].

Anesthesia should be induced carefully, avoiding hemodynamic fluctuations, hypoxia, and hypercarbia. While intravenous anesthesia with propofol may have some advantage in terms of lower ICP, there are no good data to support the use of intravenous over inhaled anesthetic agents. Increased intraoperative ICP due to inadvertent hypercarbia and improper positioning must be avoided. ICP should be closely monitored and the anesthesiologist prepared to treat intraoperative intracranial hypertension urgently.

Future Directions

There is paucity of perioperative, especially intraoperative, data on TBI management. Limited data also exist on the effect of anesthetic agents on the histopathological features of TBI, and further investigation is warranted to better characterize the impact of anesthetic agents on the injured brain. Anesthesiologists will need to partner with other disciplines to conduct larger, multi-centric studies to better guide anesthetic management. In order to formulate detailed clinical management for the very dynamic perioperative period, such studies will need to characterize the injury itself, bear in mind that TBI is a heterogeneous disease process, and collect imaging and biomarker data in addition to anesthetic details. Common data elements for research into the intraoperative TBI management have been developed [69], and future studies should incorporate them to allow uniform reporting as well as potential pooling of data. Meanwhile, perioperative management of TBI should focus on adherence to multidisciplinary, consensus guidelines.

Conclusion

The perioperative period is crucial in the continuum of TBI management. Perioperative management goals include facilitating early cerebral decompression, providing balanced anesthesia for surgery, maintaining adequate cerebral perfusion by optimizing systemic and intracranial hemodynamics, and aggressively avoiding secondary insults. Multimodal neuromonitoring should be continued in the perioperative period, particularly during extracranial

surgery in TBI patients with polytrauma. While further investigation to characterize the impact of anesthetic agents on the injured brain and their effect on clinical outcomes is awaited, perioperative management should focus on adherence to multidisciplinary, consensus guidelines.

Compliance with Ethics Guidelines

Conflict of Interest Nelson Nicolas Algarra and Deepak Sharma declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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