Intractable intracranial hypertension, mechanisms, monitoring, and rescue therapies

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- A step-by-step approach to treatment escalation, known as the “staircase approach” , aiming to obtain normal ICP values and adequate CPP as well as to reduce the risks of secondary damage is recommended for ICP management.
- Two different approaches have been described to manage severe TBI patients, depending on the standard of care, resources-limit, and expertise:

(1) pursuing the indications of inv-ICP monitoring,

(2) following brain imaging and clinical examination to escalate therapies.

TBI

- Inv-ICP placement: patients with pathological findings on CT and a GCS< 8, or impossibility to perform the neurological examination

- Patients with normal CT-scan with unavailable neurological examination and two or more of the following risk factors: age > 40 years, HTN, and abnormal flexion/extension in response to pain.

- HICP is defined as an increase in ICP over 20–22 mmHg, while in non-invasively monitored patients HICP can be suspected when one major or two minor criteria are met.

- Major criteria: compressed cisterns (CT classification of Marshall diffuse injury III), midline shift of more than 5mm (Marshall diffuse injury IV), and non-evacuated mass

- Minor criteria include GCS motor score ≤ 4, pupillary asymmetry, altered pupillary reactivity, midline shift 0–5mm, and/or lesion of 25 or less cm3 (Marshall diffuse injury II).

- Refractory HICP is defined as intracranial pressure that exceeds 22–25 mmHg for 30 min, or 30 mmHg for 15 min ,or 40 mmHg for 1 min.

Table 3 The Marshall classification system of TBI

Class		Description
I	Diffuse injury I (no visible pathology)	No visible pathology was seen on CTH
II	Diffuse injury II	-Midline shift of 0 to 5 mm -Basal cisterns remain visible -No high or mixed-density lesions > 25 cm^3
III	Diffuse injury III (swelling)	-Midline shift of 0 to 5 mm -Basal cisterns compressed or completely effaced -No high or mixed-density lesions > 25 cm^3
IV	Diffuse injury IV (shift)	Midline shift > 5 mm No high or mixed-density lesions > 25 cm^3
V	Evacuated mass lesion	Any lesion evacuated surgically
VI	Non-evacuated mass lesion	-High or mixed-density lesions > 25 cm^3 -Not surgically evacuated

Non TBI

- ICP and CPP monitoring should be used in SAH, ICH, and other non-TBI conditions in patients who are at risk of HICP based on clinical and/or imaging features (low quality of evidence).
- ICP monitoring should be considered for patients at high risk for developing hydrocephalus (moderate quality of evidence).
- All poor grade SAH patients should be monitored and be considered for multimodality monitoring (low quality of evidence).
- The use of EVD is the preferred method to monitor ICP in the setting of hydrocephalus in ICH or SAH patients (low quality of evidence)

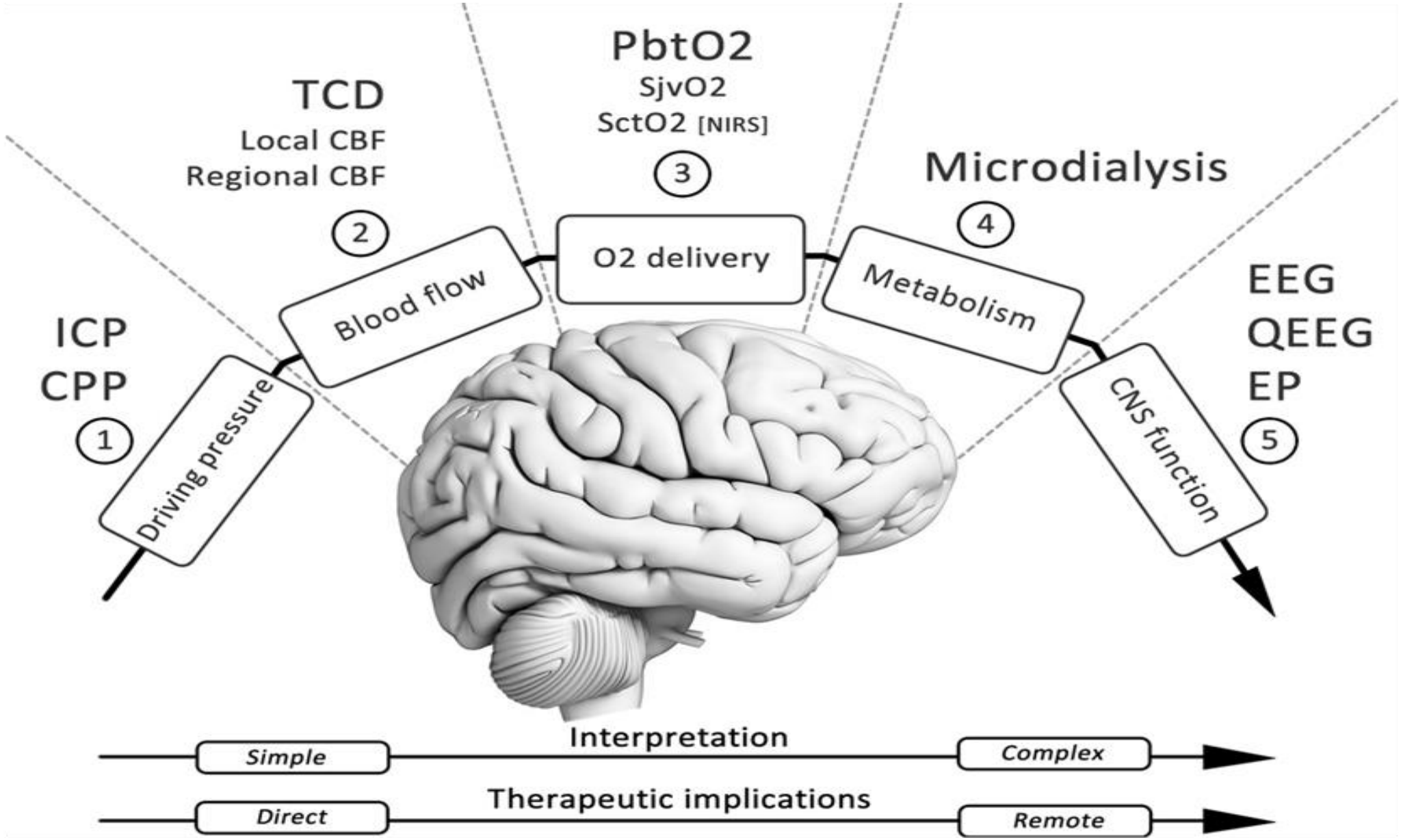
- Intraparenchymal ICP monitors and EVDs are equally reliable in providing a measure of ICP with the understanding that device location relative to a lesion is a major determinant of ICP (moderate quality of evidence).
- • Non-TBI patients who require monitoring should receive an invasive device (either intraparenchymal or intraventricular) rather than a non-invasive device (low quality of evidence).
- • Non-invasive devices do not serve as reliable ICP monitors, however, they may be used to estimate ICP when invasive ICP monitoring is not feasible (low quality of evidence).
- • Ipsilateral monitoring is preferred when the goal is to reduce ICP in the lesioned hemisphere (moderate quality of evidence)

- Persistent or refractory intracranial hypertension may be useful as a prognostic marker in non-TBI patients (low quality of evidence).
- ICP monitoring should be initiated or maintained for patients who undergo hemicraniectomy in the setting of cerebral edema (low quality of evidence).
- A combination of ICP and CPP monitoring along with waveform analysis, ICP variability and the integration of other physiologic data may help improve outcomes (weak quality of evidence).
- For patients at risk for HICP use of continuous ICP monitoring to alert clinicians is preferred over intermittent assessment (moderate quality of evidence).

Advanced Monitoring

Table 1. Advances in monitoring techniques

Technique	Description	Applications	Recent Innovations
Continuous electroencephalogram	Real-time monitoring of brain activity	Nonconvulsive seizures, brain function assessment	Quantitative electroencephalogram, improved sensors [1-10]
Intracranial pressure monitoring	Measurement of pressure within the cranial cavity [4]	Traumatic brain injury, subarachnoid hemorrhage management	Less invasive devices, multimodal monitoring systems [12-15]
Functional magnetic resonance imaging	Imaging technique that measures brain activity through blood flow changes	Brain function, injury assessment	Enhanced resolution, real-time imaging [35-39]
Computed tomography perfusion imaging	Measures cerebral blood flow and perfusion	Stroke detection and management	Faster imaging, improved contrast agents [44]


PbtO2
SjvO2
SctO2 [NIRS]
3
TCD
Local CBF
Regional CBF
2
Microdialysis
4
ICP
CPP
1
Blood flow
O2 delivery
Metabolism
EEG
QEEG
EP
5
Driving pressure
CNS function
Interpretation
Simple
Complex
Therapeutic implications
Direct
Remote

- The indication for initiating HICP treatment is clear in case of inv-ICP monitoring (ICP > 20–22 mmHg), but the clinical examination and CT-based approach for non-invasively monitored patients is less straight forward.
- Based on clinical and radiological findings, escalation of therapy should be considered in case of neuroworsening, no improvement or impairment on CT scan, or no response to initial therapy.

- Neuroworsening is defined as a decrease in GCS motor score>2, loss of pupillary reactivity, new pupillary asymmetry, and/or deterioration of neurological status

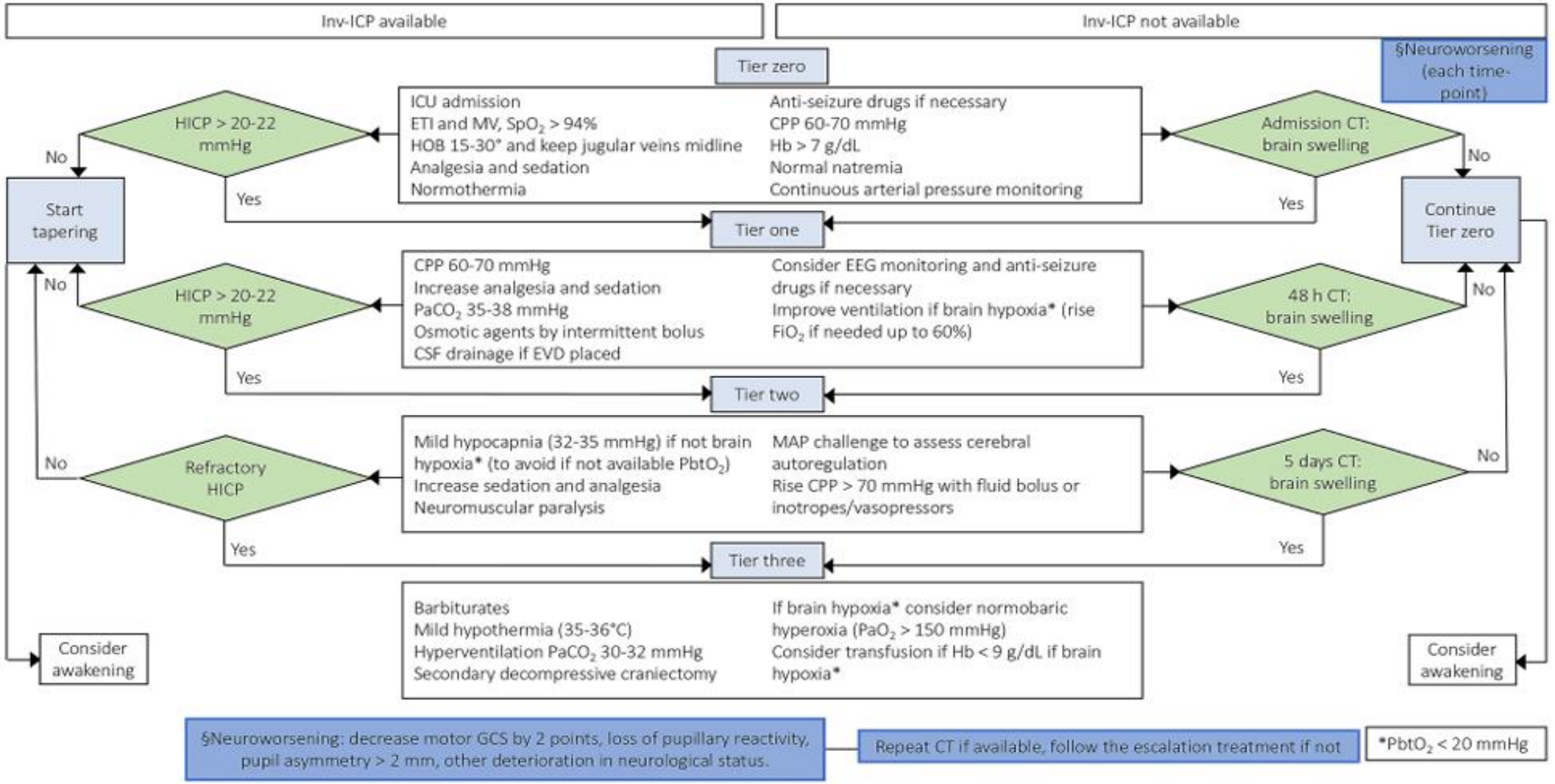


FIGURE 2 | Escalation management for controlling ICP in TBI patients with or without inv-ICP monitoring. Escalation of care in patients with HICP or neuroworsening/radiological impairment [Modified from Hawryluk et al. (9) and Carney et al. (4)]. inv-ICP, invasive intracranial pressure; ETI, endotracheal intubation; MV, mechanical ventilation; CPP, cerebral perfusion pressure; Hb, hemoglobin; $PaCO_2$, partial pressure of carbon dioxide; CSF, cerebral spinal fluid; SpO_2, peripheral saturation of oxygen; HOB, head of the bed; CT, computed tomography; HICP, intracranial hypertension; $PbtO_2$, brain tissue oxygen tension; EVD, external ventricular drainage; EEG, electroencephalography; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen; GCS, Glasgow coma scale.

Tier Zero

- Basic interventions that should be implemented irrespective of ICP elevation, and that can be pursued in all sub-populations of neurocritical care patients.
- Include ICU admission, endotracheal intubation and MV, serial neurological evaluation, head-up position (15–30◦), analgesia for pain management, sedation to prevent ventilator-patient asynchronies, normothermia, central line placement, end-tidal CO2 monitoring, a CPP threshold of 60mmHg, hemoglobin >7 g/dL, normal values of serum sodium, an arterial line for invasive continuous pressure monitoring, SpO_2 ≥94% and glycemic control.

Tier one to three

- Interventions initiated only incase of HICP:
- (1)CPP maintenance (60-70 mmHg), analgesia and sedation, intermittent bolus administration of osmotic agents, CSF drainage if an EVD device has been placed, PaCO2 between 35 and 38 mmHg, EEG monitoring, and prophylactic anticonvulsants if risk is deemed high
- (2) mild hypocapnia (32–35mmHg),neuromuscular paralysis, MAP challenge to assess autoregulation using inotropes/ vasopressors, and use of inotropes/vasopressors when necessary if autoregulation is intact
- (3) barbiturate coma, mild hypothermia (35–36◦C), hyperventilation with a goal of 30-32 mmHg $PaCO_2$, and secondary decompressive craniectomy

Sedation and analgesia

- Since the main problem of HICP is the decrease in CBF and tissue perfusion, the metabolic effect of sedatives on oxygen consumption becomes marginal.

- The use of sedatives and analgesics is essential to protect the brain in the acute phase (within 48h of injury), and to control HICP.

- The ideal sedative in TBI patients would be able to reduce the $CMRO_2$, while maintaining CBF/$CMRO_2$ coupling, CPP, cerebral autoregulation, and not raising ICP

- In presence of HICP, propofol, fentanyl, and rocuronium are used in more than 80% of cases, while midazolam and ketamine are less frequently used.
- Propofol and midazolam seem effective for ICP control, although propofol shows greater effects on brain metabolism.
- These effects are dose-dependent: at 5mg/kg/h it can cause burst suppression. Propofol doses can be increased if the EEG does not suggest metabolism suppression and ICP control is not achieved.
- Midazolam can be suggested over propofol in case of hemodynamic instability, but the need for higher doses for ICP control could lead to accumulation, leading to prolonged coma, MV, and ICU LOS.

- Ketamine when compared with opioids does not increase ICP and provides an optimal hemodynamic stability, reducing the need for vasopressors.
- ketamine is not included among the first-line sedatives for ICP control but may be (1–5 mg/kg/h) together with other sedatives to reduce their doses.
- A classical protocol in patients with HICP may include propofol 4–6 mg/kg/h and fentanyl 1–4 μg/kg/h, plus vasopressors as needed for the maintenance of CPP.
- Dexmedetomidine could be a useful adjunct in the management of refractory HICP, reducing the need for hyperosmolar fluid without compromising hemodynamics

Table 6 Medication physiologic effects and key points [23, 24]

Medication	Intracranial pressure (ICP)	Cerebral blood flow (CBF)	Cerebral blood volume (CBV)	Cerebral metabolic rate (CMR)	Keypoints
Barbiturates	↓	↓	↓	↓	
Benzodiazepines	↓ or NC	↓	↓	↓	-Neutral hemodynamic profile -anxiolytic and anticonvulsant effects
Etomidate	↓	↓	↓	↓	-Mild hemodynamic profile -For the normotensive/hypertensive patient
Ketamine	↑	↑	↑	↑ or NC	-Can be neuroprotective without increasing cerebral oxygen consumption -Has sympathetic stimulation properties that may aid in increasing MAP and CPP -For the hypotensive patient
Opiates	NC	NC	↓ or NC	NC	-Neutral hemodynamic profile -Can blunt the sympathetic response of elevated MAP and heart rate in RSI -For the normotensive/hypertensive patient
Propofol	↓	↓	↓	↓	-Decreases cerebral metabolic demand and cerebral blood volume -For the normotensive/hypertensive patient

* Decrease (↓), increase (↑), no change (NC)

Hyperosmolar therapies

- Bolus administration of hyperosmolar therapy represents a fundamental step of the “staircase approach,”
- Continuous infusion of hyperosmolar drugs is not recommended

Salt vs sugar

- Negative effects of mannitol include dehydration, hypovolemia, prolonged QTc interval, arrhythmias, and myocardial ischemia and acute renal failure, especially in patients with hypo-or normonatremic hyperosmolality.

Table 5 Sodium concentration, osmolarity, and bolus dosing for hyperosmolar agents [4, 20, 21]

Hyperosmolar agent	Sodium Concentration (mEq/L)	Osmolarity (mOsm/L)	Bolus range dosing
Mannitol 20%	n/a	1098	0.5–1.0 g/kg
Mannitol 25%	n/a	1375	0.5–1.0 g/kg
3%	513	1027	1.4–2.5 mL/kg
7.5%	1282	2566	1 mL/kg
23.4%	4004	8008	30 mL

* *mEq* milliequivalents, *mOsm* milliosmole, *L* liter, *g* gram, *mL* milliliters, *kg* kilogram

CSF drainage

- In case of inv-ICP monitoring with an EVD system, CSF drainage represent an effective technique to reduce ICP, but there is no strong evidence of ICP long-term reduction.

- Intraventricular ICP is the first and oldest system of inv-ICP monitoring described, and still represents the more reliable device capable to detect ICP and to assess intracranial compliance

- The device is usually placed in the frontal horn of the ventricle through the Kocher point, 2cm anteriorly to the coronal suture and 2.5–3cm laterally from the midline, directed toward the intersection point between the sagittal plane on the medial canthus of the ipsilateral eye and the coronal plane on the external auditory meatus

- Complications associated to the placement of intraventricular inv-ICP device may include technical problems misplacement, dislocation, kinks, obstruction from debris, hemorrhage and infection.

- In Intraventricular device is often difficult to position in young patients because of the smaller ventricle volume, and in TBI patients with HICP in whom the ventricular system is collapsed as a compensatory mechanism.

- Ventricular inv ICP monitoring is usually considered the “gold standard,”

$PaCO_2$

- Both hypo and hypercapnia are associated with poor outcomes after TBI.
- In “tier zero,” $PaCO_2$ should be maintained between 35-38 mmHg, while prophylactic moderate hyperventilation in HICP should be weighted on risk/benefit to patients, considering harmful for GCS < 4–5, as $PaCO_2$ levels between 20-25 mmHg correspond to a 40–50% decrease in CBF.
- On pre-hospital TBI cares avoid hyperventilation within the first 24h following TBI, except in clear case of refractory HICP or cerebral herniation.
- On the other side, a brief period (15–30min) of hyperventilation in case of refractory HICP, targeting PaCO2 of 30–32/30–35 mmHg may be appropriate.

Metabolic Suppression Management (Barbiturates)

- A state of burst suppression is not the goal of barbiturates, and if it appears, no further dose increases are indicated. Barbiturates also decrease cardiac output, thus modulating cerebral metabolic demand, with no effects on mortality or disability.

- Higher efficacy of thiopental when compared to pentobarbital. pentobarbital: 5–7 to 10 mg/kg, and thiopental a loading dose of 15 mg/kg followed by continuous infusion of 100 mg/kg/day .

Decompressive craniectomy

- DC consists in the removal of a portion of skull in order to treat refractory HICP and represents the most aggressive step of the “staircase approach”.
- When the bone flap is not replaced after surgery for the evacuation of an intracranial mass lesion, DC is named “primary,” while it is considered “secondary” when DC is performed later after other treatments have failed.
- DC can be performed as a large frontal-temporal-parietal flap (at least 12 × 15cmdiameter) or as a bifrontal flap.

CONTUSION <2%



BBB mainly closed
Osmolarity is the driving force of edema formation
Autoregulation is efficient

First-tier therapy for HICP
- CSF drainage
- Increase CPP
- Increase Osmolarity (hypertonic saline 40 mL/30 minutes)

CONTUSION >2%



BBB damaged
Increase of ICP and Osmolarity worsen edema
High risk of vasogenic edema in the contused area

First-tier therapy for HICP
- CSF drainage
- Reinforce sedation
- Hypothermia?
- Corticosteroids?
- Surgery

FIGURE 5 | A former point-of-view for novel therapeutic approaches. The figure depicts a proposed therapeutic approach based on a former point-of-view no longer investigated and that should be reinterpreted in light of the progresses in TBI research. The image on the left represents a CT-scan with a contusion <2%. The suggested therapies for this condition are described below. The image on the right represents a CT-scan of a contusion of more than 2%. The suggested therapies are described below. BBB, blood brain barrier; HICP, intracranial hypertension; CSF, cerebral spinal fluid; CPP, cerebral perfusion pressure.

Tapering therapies after the control of intracranial HTN

- Once HICP is controlled, the aggressive therapies applied following the “staircase approach” should be carefully tapered in order to avoid secondary brain damage induced by excessive brain metabolism suppression, reduced oxygen delivery, and impaired systemic hemodynamics with dangerous consequences to the brain

Cranioplasty

- Complications after cranioplasty include wound complications, infection, hydrocephalus, epidural or subdural hematoma, new-onset seizures.

- The optimal timing for cranioplasty after DC is a matter of debate, considering its hypothetical influence on postoperative infection.

- There is a growing trend to perform earlier cranioplasties (15–90 days after DC), although there is only low grade evidence (Class IIb, Level C) to support this intervention.

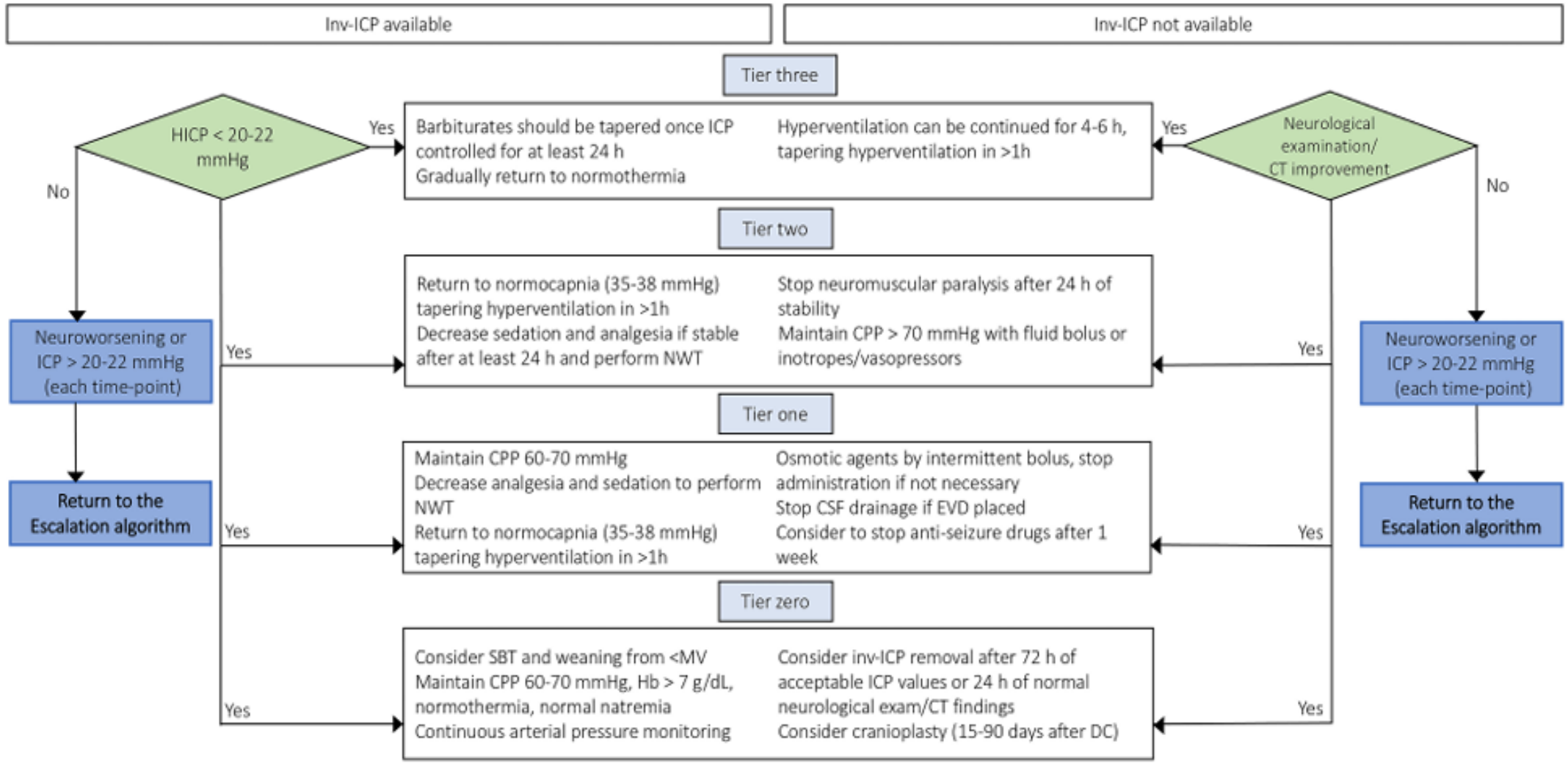


FIGURE 3 | De-escalation management after controlling intracranial hypertension in TBI patients with or without inv-ICP monitoring. De-escalation management for controlling intracranial hypertension basing on available current evidences [Modified from Stocchetti et al. (3), Hawryluk et al. (9) and Carney et al. (4)]. inv-ICP, invasive intracranial pressure; CPP, cerebral perfusion pressure; Hb, hemoglobin; $PaCO_2$, partial pressure of carbon dioxide; CSF, cerebral spinal fluid; CT, computed tomography; HICP, intracranial hypertension; EVD, external ventricular drainage; NWT, neurological wake-up test.

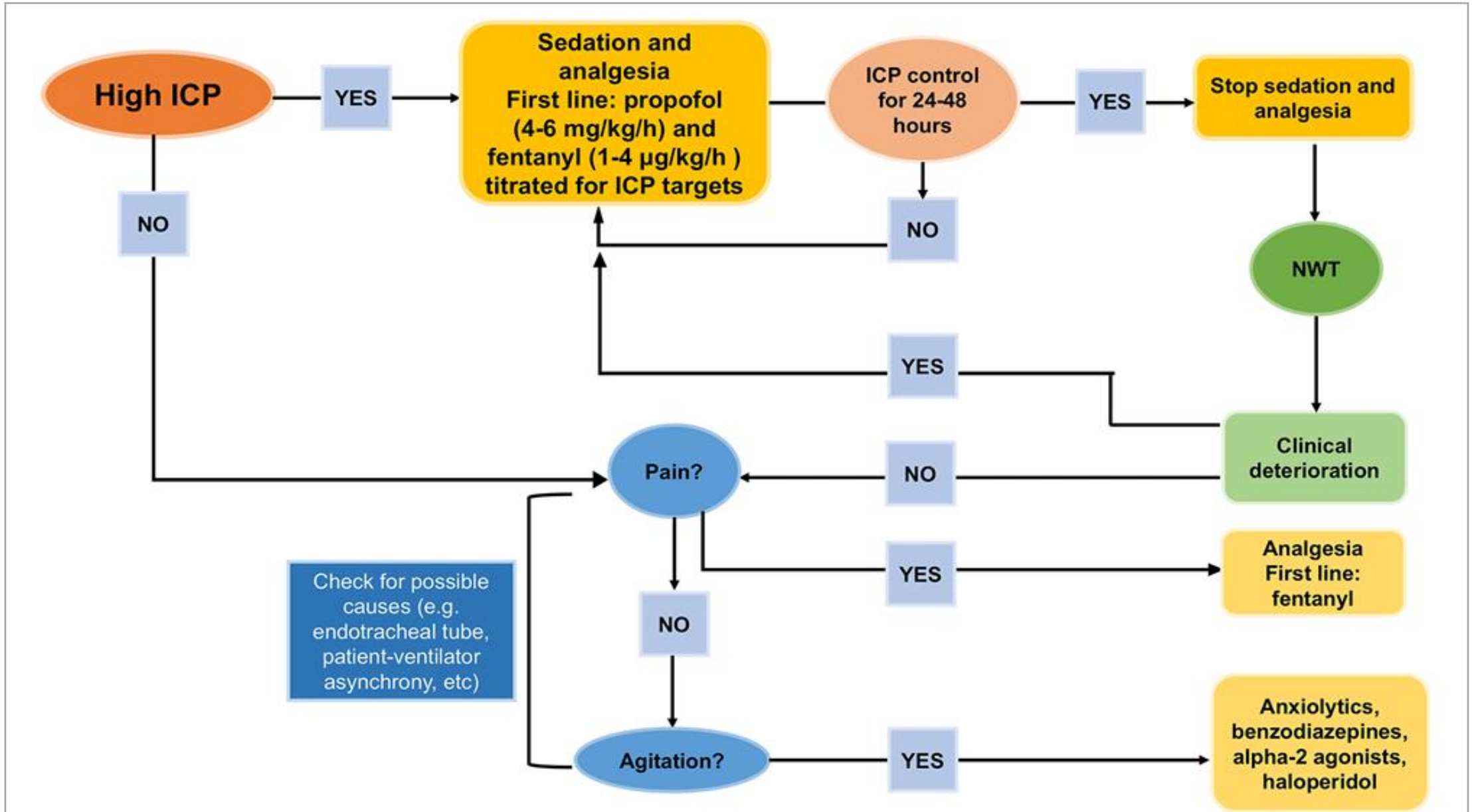


FIGURE 4 | How to de-escalate from sedatives and analgesics. Proposal for de-escalating sedatives and analgesics after intracranial hypertension control [Modified from Oddo et al. (17)].

Thank you!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Everything is
theoretically impossible,
until it is done.
Robert A. Heinlein
hellobio.