Risk Factors and Mechanisms of Postoperative Delirium After Intracranial Neurosurgical Procedures

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Postoperative delirium (POD) is a condition characterized by cerebral dysfunction or failure and associated with high morbidity and mortality, prolonged intensive care unit and hospital stay, increased costs and long-term disability. The risk factors can be divided into three categories: preoperative, intraoperative, and postoperative. POD is underrecognized, underdiagnosed, and undertreated condition which can also lead to potentially life-threatening conditions. Prevention and treatment of POD include adequate perioperative pain control, maintenance of optimal blood pressure, water-electrolyte balance, hypo- and hyperglycemia, sleep hygiene. Despite POD has been extensively studied in various types of surgery, there is not enough evidence on POD in intracranial neurosurgery. Patients undergoing open craniotomy might be at particular risk because on top of the above-mentioned factors, they also might have a direct neurosurgical brain injury. Future research on the POD in neurosurgical patients after intracranial interventions is needed. A bibliographic search was performed in the MEDLINE and PubMed virtual library. The following descriptors were used: POD, neurosurgery, anesthesia, and POD, postoperative pain management and POD, water and electrolyte imbalance and POD, neurochemistry of POD. We included in this review original and review articles in the English language. Majority of non-neurosurgical patients have multiple risk factors for POD (preoperative, intraoperative, and postoperative); patients undergoing intracranial neurosurgery on top of that might have additional risks associated with neurosurgical pathology (brain tumor, cerebral hemorrhage, and severe traumatic injury) as well as neurosurgery-induced brain injury can also appear to be a contributing factor.

Keywords: postoperative delirium, neurosurgical procedure, risk factors, neurocritical care

Introduction

Delirium is defined as an “organ failure of the brain” similar to organ failure conditions of severe multi-organ complications.1 Postoperative delirium (POD) is one of the most frequent neuropsychiatric complications after surgery in elderly patients.2 By POD after intracranial neurosurgical procedure, we imply the transient and reversible mental dysfunction manifesting clinically with different neuropsychiatric abnormalities which can be caused by multiple factors including neurosurgery-related brain injury. By intracranial neurosurgical procedure, we imply any type of procedure associated with manipulation on the brain (open craniotomies—tumor removal; minimally invasive neurosurgical procedures—endoscopic...
skull-based surgery, interventional cranial procedures, stereotactic surgery). POD occurs in the early post-operative period, associated with sepsis and worsens outcomes both short and long term—high postoperative complication rates, higher morbidity and mortality rates, prolonged intensive care unit (ICU) and hospital stay, increased ICU-related costs and medication use, long term disability, and loss of independence.\textsuperscript{3,4} Patients with POD have a greater risk of developing dementia and persistent cognitive dysfunction compared to the patients without delirium.\textsuperscript{5} The incidence of POD varies from 10% to 70% depending on the type of surgery, patient age (more prevalent in the elderly), and presence of comorbidities.\textsuperscript{6} The elderly population is of particular concern, as a percentage of the aging population is increasing in most countries and the societal burden of this problem is expected to increase.\textsuperscript{7} The purpose of this review is to provide the perspective on POD after intracranial neurosurgery and to summarize the risk factors for POD in intracranial neurosurgery patients.

**Methods**

**Search Strategy**

A bibliographic search was performed in the MEDLINE, PubMed, and Google Scholar (from 1976 to 2019). The following descriptors were used: (1) etiology of POD; (2) etiology of POD in neurosurgery; (3) anesthesia and POD, postoperative pain management and POD; (4) water and electrolyte imbalance and POD, water and electrolyte imbalance in neurosurgical and neurological patients; (5) electrolyte imbalance in neurocritical care unit, (6) duration of neurosurgical vs. non-neurosurgical procedures (operations); (7) surgically-induced brain injury; (8) pathogenesis of POD. After extraction and analysis of the available risk factors for delirium, authors analyzed whether these risk factors are frequently present in neurosurgical patients (we used this methods since there was no much evidence on POD in neurosurgery). Our hypothesis was that if these risk factors (cerebrovascular diseases, stroke, brain tumor, etc.) are more common among neurosurgical patients, the incidence of delirium in neurosurgical patients can be even higher (Figure 1).

**Risk Factors for Postoperative Delirium**

The risk factors might be divided into preoperative, intraoperative, and postoperative (Figure 2), although most patients have multiple risk factors.\textsuperscript{8}

**Preoperative Period**

The most common predisposing general preoperative factors for POD are advanced age, cognitive and functional impairment, the presence of comorbidities, such as alcoholism, neurocognitive disorders (e.g., dementia, psychosis, and depression), the use
of psychopharmacological agents. Other comorbid conditions include diabetes mellitus, hypertension, fluid and electrolyte disturbances, chronic renal failure, anemia, chronic steroid treatment, and significant weight loss have also been associated with POD.

Preoperative Risks for Postoperative Delirium in Neurosurgical Patients

In neurosurgical patients, the number of preoperative risk factors can be even greater. Thus, neurosurgical patients can have numerous neurological and neurosurgical conditions (diseases) that can contribute to the development of POD, such as acute cerebral injuries, cerebral ischemia, neoplastic brain disease, intracranial hemorrhage, subarachnoid hemorrhage (SAH) hydrocephalus, brain infection, and preexisting cognitive impairment (Table 1). These patients have multiple risk factors for POD even before they are admitted to the hospital and medical and/or surgical interventions are initiated. Thus, some medical conditions such as cognitive impairment, water and electrolyte abnormalities, diseases such as brain tumors, SAH, ischemic heart disease, diabetes, hypertension, arrhythmias, and epilepsy are common in neurosurgical patients (Table 1). Many of those patients take medications (which in turn can increase the risk of POD) to control their diseases, such as antineoplastic medication, antidepressants, and benzodiazepins (Table 1). Electrolyte disorders are also common in the preoperative period and have been shown to be the most frequent systemic complications in patients with neurologic diseases. Among electrolyte disorders, hyponatremia is one of the most common conditions in neurological patients which has been frequently reported in patients with delirium. Neurocognitive disorders are also commonly diagnosed in neurosurgical patients. According to Tucha et al.,

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about 91% of patients with brain tumor demonstrated impairment in at least one area of cognition and about 71% had impairment in more than three areas of cognitive performance. Many patients who have indications for the intracranial procedure, also frequently have the existing disorder of cerebral physiological processes which may increase the risks of POD, such as elevated intracranial pressure, a diffuse, or regional disorder of cerebral circulation. It appears that neuroanatomical location of the pathology (e.g., cortical and subcortical) also can lead to POD. Naidech et al. showed that the location of intracranial hematoma within the right cerebral subcortical white matter or parahippocampus was directly associated with delirium.

### Intraoperative Period

The extent of surgical intervention, duration of surgery and anesthesia, choice of anesthetic drugs, amount of intraoperative blood loss, the occurrence of hypoxemic or hypotensive events were all found to be associated with POD. Echigoya et al. suggested that hypotension leads to cerebral hypoperfusion and ischemia with resultant delirium. Marcantonio et al. demonstrated a correlation between the degree of intraoperative blood loss, hematocrit less than 30%, and the need for blood transfusions and POD suggesting a mechanism related to a reduction of oxygen delivery to the brain during massive blood loss. They also found the correlation between POD and intraoperative hypotensive as well as hypertensive events and sinus tachycardia or bradycardia. The perioperative blood loss and hypotension can cause inadequate brain perfusion and brain hypoxia and predispose to POD.

### Intraoperative Period in Neurosurgical Patients

Hypothetically, neurosurgical patients are at higher risk for developing cerebral ischemia or hypoperfusion than general surgical patients (taking into account that the elevated cerebral pressure and reduced cerebral perfusion are common among neurosurgical patients). Many intraoperative factors including blood loss, tissue injury, medication, and pain can activate the immune cells and trigger the production of inflammatory mediators. In some cases, even aseptic inflammation can be disseminated resulting in systemic inflammation and elevated levels of cytokines in the blood which might contribute to POD. It has been found that the patients with delirium had higher interleukin-6 and interleukin-8 levels than without delirium. Animal models have shown that peripheral injection of lipopolysaccharide activates inflammatory cascade leading to blood-brain barrier damage, over-expression of adhesion molecules and infiltration of leukocytes into the cerebral tissue.

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**Table 1. Risk factors and mechanism of postoperative delirium in neurosurgery**

<table>
<thead>
<tr>
<th>Preoperative risk factors for POD</th>
<th>Mechanism/description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe traumatic brain injury</td>
<td>Contusion, bleeding, edema, cerebral ischemia, elevated ICP, reduced CPP, neuroinflammation, oxidative stress, excitotoxicity</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>Depression, use of psychoactive medication (antidepressants, benzodiazepines), use of anticancer medication, electrolyte abnormalities, pain, decreased cerebral acetylcholine production, cerebral ischemia, elevated ICP, reduced CPP, neuroinflammation, oxidative stress</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Cerebral ischemia, excitotoxicity, cerebral edema, neuroinflammation, oxidative stress, cerebral edema, elevated ICP, reduced CPP, BBB dysfunction</td>
</tr>
<tr>
<td>SAH</td>
<td>Bleeding, cerebral vasospasm, cerebral ischemia, neuroinflammation, cerebral edema, elevated ICP, reduced CPP, electrolyte abnormalities.</td>
</tr>
</tbody>
</table>

**Neurosurgery-induced brain injury**

<table>
<thead>
<tr>
<th>Cortical incision</th>
<th>Bleeding, edema, direct injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retraction of the brain lobes</td>
<td>Thermal injury of the cerebral tissue, brain edema</td>
</tr>
</tbody>
</table>

Abbreviations: BBB, blood–brain barrier; CPP, cerebral perfusion pressure; ICP, intracranial pressure; POD, postoperative delirium; SAH, subarachnoid hemorrhage.

This table demonstrates diseases, events, and procedures that can contribute to development of POD. The most common “universal” events that take place to some extent almost in all neurosurgical diseases as well as are cerebral bleeding, cerebral edema, ischemia, elevated ICP, reduced CPP, excitotoxicity. Each of these events plays certain role in the pathogenesis of POD.
has been shown that neurosurgical patients frequently develop systemic inflammatory response syndrome. Thus, Boehme et al. found that as many as 20% of patients with intracerebral hemorrhage develop systemic inflammatory response syndrome. Apart from systemic inflammation many other conditions such as hypoxic-reperfusion injury in stroke can lead to disruption of blood-brain barrier and increase the risk of delirium.

**Surgery-Induced Brain Injury**

There is still not enough evidence about POD in neurosurgical patients undergoing intracranial surgery, whether certain types of neurosurgical procedure can result in procedure-related brain injury and increase the risk of POD. Weed et al. reported that the incidence of POD in major head and neck surgery was 17%, whereas Zipser et al. estimated it to be as high as 32.4%. In fact, craniotomy is frequently associated with direct brain damage such as cortical incision, retraction of the brain lobes, electrocoagulation which can result in local bleeding and edema. However, the consequences of neurosurgery-related cerebral injury and its relations to POD have not been extensively studied yet. It appears that some neurological pathologies even without additional neurosurgery-induced brain injury can trigger POD but minimally invasive interventions such as neuroendovascular procedures lead to less prominent neurocognitive dysfunction compared to traditional neurosurgical procedures requiring craniotomy. Hadjivassiliou et al. in their study focusing on cognitive dysfunction after coiling or clipping of aneurismal SAH showed that both groups (with patients having their aneurisms either coiled or clipped) had impairment in all cognitive domains, compared with age matched healthy subjects; however, in the surgical group (coiling) neurocognitive outcome was poorer compared to the endovascular group (clipping), which can be explained by more severe structural damage.

**Anesthesia and Postoperative Delirium**

There are multiple anesthesia-related risk factors among neurosurgical patients that potentially can influence POD. It was found that deep sedation during surgical procedures under regional anesthesia can increase risk of POD. It has also been demonstrated that light propofol-based sedation during spinal anesthesia was associated with a decrease of POD prevalence by 50% compared to deep propofol sedation.

Furthermore, prolonged administration of anesthetics and deep level of anesthesia than needed can also contribute to POD. Furthermore, Ishii et al. found that propofol-based compared to sevoflurane-based anesthesia is associated with a lower incidence of POD in elderly patients. Opioids have been also found to be implicated with POD. Thus, intravenous dose-dependent fentanyl administration during the neurosurgical procedure was found to have a strong correlation with development of POD in comparison with remifentanil. Ravi et al. showed that the duration of surgery was associated with an increased risk of POD in hip fracture patients. Hypercapnea, anemia, and hypothermia contribute to disruption of cerebral autoregulation. Major surgery increases the risks of POD which can be explained by the fact that the major surgery is associated with higher total doses of anesthetics used, the degree of surgical trauma and total blood loss. Therefore, it was recommended by Ravi et al., in order to reduce the risks of POD, major surgeries such as hip fractures should be managed by experienced surgeons and anesthesiologists who can finish surgery quick.

It was previously believed that anesthetic dosing during surgery does not affect the long-term outcome and the effect of the drugs is eliminated after they cleared from the body. However, nowadays more and more results show that the anesthesia-related neurocognitive dysfunction can stay for a long time after anesthesia is over and the doses of anesthetics can affect it. It appears that the optimization of depth of anesthesia and balancing of anesthetic doses which can be achieved via bispectral index (BIS)-monitoring which can potentially reduce the anesthesia-related risks of POD. Thus, Matthew et al. demonstrated that BIS monitoring-guided anesthesia in elderly surgical patients resulted in a reduction of propofol delivery by 21% and that for volatile anesthetics by 30% and reduced risk of POD and postoperative cognitive decline.

Since neurosurgical procedures are on average longer than non-neurosurgical, the BIS monitoring might be especially beneficial for minimizing POD via optimizing intraoperative anesthetic delivery using minimally effective concentrations of volatile anesthetics for long neurosurgical procedures.

**Postoperative Period**

There have been identified numerous events in the postoperative period that can trigger POD. Vaurio
et al. observed that the degree of postoperative pain levels and types of postoperative pain management have a correlation with POD. They demonstrated that severe postoperative pain predisposed to POD. There was found no difference between intravenous patient-controlled analgesia and neuroaxial blocks in terms of the development of POD. That means that the method of pain management does not play a major role and the main goal for minimizing the risks of POD is to provide adequate pain control.

Sleep in Intensive Care Unit and Postoperative Delirium

Disorder of sleep which is extremely common among critically ill patients appears to be a risk factor for POD. Poor quality and abnormality of sleep, its fragmentation is widely reported among critically ill patients. ICU environment with presence of high intensity 24-hour working personnel, constantly activated alarms, telephones, which in turn can worsen sleep in ICU settings. Sedative drugs are extensively used for sedation in ICU; however, they can also contribute to sleep disorders and delirium.

The Neurochemical Mechanisms Postoperative Delirium

Previously published studies demonstrated that the cholinergic system plays a conceptual role in the pathogenesis of POD. It has been also shown that anticholinergic drug-induced toxicity might cause delirium. As it has been already mentioned earlier, geriatric patients are at high risk of POD. Normally, aging-associated with a reduction of acetylcholine release and activity of muscarinic receptors. Thus, dopamine excess and acetylcholine deficiency play a central role in delirium. Since many neurosurgical patients have dysfunction in cholinergic or dopaminergic system due to primary neurological or neurosurgical diseases, those patients are at high risk for POD. Similarly, any drug administered during neurosurgical procedure and postoperative neurocritical care with anticholinergic activity, such as atropine, can be potential trigger for POD. Moreover, it has been suggested not use benzodiazepines, despite their sedative effect, in patients without a history of alcoholism and psychiatric illnesses. Since neurosurgical patients are more likely to have seizures and other neurological disorders, they are hypothetically more likely to take benzodiazepines and gabapentine (for management of seizures or other conditions) that non-neurosurgical patients; therefore, they can be at higher risk for POD.

Postoperative Risk Factors in Neurosurgical Patients

It has been shown that severe traumatic brain injuries cause the imbalance between catabolic and anabolic hormones and neuroendocrine disorders that can result in hyperglycemia, hyper-, hyponatremia, increased serum cortisol. Most of neurosurgical patients are more likely (than non-surgical patients) to develop neuro-endocrine and water-electrolyte balance disorders such as syndrome of inappropriate antidiuretic hormone secretion, diabetes insipidus, and POD as a consequence.

Neuroendocrine imbalances commonly result from hypothalamic-pituitary dysfunction (HPD). HPD is a known consequence of neurosurgery as well as numerous neurosurgical pathologies diseases. For example, HPD has been reported to be present in 55% of the patients with subarachnoid embolism. Hypoponatremia is a common complication in neurosurgical patients in postoperative period. The most common causes of hyponatremia in the neurocritical care unit include neurological pathologies, such as hypophysectomy for treatment of pituitary tumors, traumatic brain injury, SAH. Nevertheless, BBB is supposed to protect the brain against detrimental circulatory chemicals; however, primary brain injuries (hypoxia, cerebral edema) which are common in neurological and neurosurgical patients disrupt the integrity of BBB and make the brain more vulnerable to chemokine-induced brain injury. In turn, circulatory chemokines are able to disrupt BBB even in the intact brain.

Management of Postoperative Delirium

Recent systematic review and meta-analysis showed that BIS-monitoring, dexmedetomidine and antipsychotics can reduce the rates of POD. Supposedly, the best way to manage POD is its prevention. In accordance with the studies that have been conducted to date, the most promising methods of preventing POD include an adequate perioperative pain management, optimal depth of anesthesia, maintenance of acid-based balance, serum glucose, electrolytes, the hemoglobin within the normal ranges, normalization of good sleep quality, early activation, and rehabilitation. In neurosurgery, minimally invasive modalities (endovascular interventions) appear to be...
associated with less potential to cause structural cerebral injuries and subsequently cognitive decline and delirium.

**Future Directions of Research**

There is very weak evidence on POD in neurosurgical patients. Future research might be focused on incidence, mechanisms, risk factors, prevention, and management of POD in neurosurgical patients. At the moment, there are numerous minimally invasive neurosurgical procedures and since it has been demonstrated that endovascular minimally invasive procedures can be more beneficial in terms of POD risk reduction due to less structural injury, future research should yield more solid evidence on this matter. The comparison of open craniotomies, endovascular interventions, and stereotactic radiosurgery (gamma knife) in terms of POD will be needed. Effective perioperative pain management (including regional anesthesia in neurosurgery) seems to be an interesting and promising research area. Since cognitive dysfunction (especially in elderly population) is becoming an important healthcare issue, another potentially attractive area for research is transition of POD to long-term postoperative cognitive decline after intracranial procedures.

**Conclusion**

POD is a very frequent complication in postoperative period. Majority of non-neurosurgical patients have numerous (preoperative, intraoperative, and postoperative) risk factors for POD, whereas neurosurgical patients on top of that frequently have additional risks associated with neurosurgical pathology (brain tumor, cerebral hemorrhage, and severe traumatic injury) as well as neurosurgery-induced brain injury might also appear to be a contributing factor. Surprisingly, POD has not been extensively studied in neurosurgery. High-quality prospective observational studies are warranted to establish incidence, risk factors, clinical characteristics, diagnostics and management as well as long term consequences.

**Authors’ Contributions**

Dmitriy Viderman participated in the conception and design of the study, collected the literature, prepared the tables, and wrote the manuscript. Dmitriy Viderman, Evgeni Brotfain, Federico Bilotta and Agzam Zhumadilov reviewed and edited the manuscript and approved the final version.

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