

Review

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[Hyun Jung Koh](#) and [Jin Joo](#) *

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Review

The Role of Cytokines in Perioperative Neurocognitive Disorders: A Review in the Context of Anesthetic Care

Hyun Jung Koh and Jin Joo *

Department of Anesthesiology and Pain Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 06591, Korea

* Correspondence: huejung@catholic.ac.kr

Abstract: Perioperative neurocognitive disorders (PNDs), including postoperative delirium, delayed neurocognitive recovery, and long-term postoperative neurocognitive disorders, present significant challenges for older patients undergoing surgery. Inflammation is a protective mechanism triggered in response to external pathogens or cellular damage. Historically, the central nervous system (CNS) was considered immunoprivileged due to the presence of the blood–brain barrier (BBB), which serves as a physical barrier preventing systemic inflammatory changes from influencing the CNS. However, aseptic surgical trauma is now recognized to induce localized inflammation at the surgical site, further exacerbated by the release of peripheral pro-inflammatory cytokines, which can compromise BBB integrity. This breakdown of the BBB facilitates the activation of microglia, initiating a cascade of neuroinflammatory responses that may contribute to the onset of PNDs. This review explores the mechanisms underlying neuroinflammation, with a particular focus on the pivotal role of cytokines in the pathogenesis of PND.

Keywords: perioperative neurocognitive disorder; postoperative delirium; postoperative cognitive dysfunction; blood–brain barrier; neuroinflammation; cytokine; anesthesia

1. Introduction

The aging population presents significant challenges for patients undergoing surgery [1]. Perioperative neurocognitive disorders (PNDs), including postoperative delirium (POD), delayed neurocognitive recovery, and postoperative neurocognitive dysfunction, are particularly concerning for older surgical patients [2]. The intricate relationship between cytokines and cognitive dysfunction involves multiple mechanisms, such as blood–brain barrier (BBB) disruption, microglial activation, and oxidative stress. It is increasingly recognized that the immune system plays a pivotal role in influencing the central nervous system (CNS) after surgical trauma, potentially contributing to the development of PND [3]. However, the underlying mechanisms remain poorly understood.

One proposed explanation for PND is an exaggerated peripheral inflammatory response in surgical patients, which leads to the release of pro-inflammatory cytokines by macrophages. These cytokines may subsequently cross the BBB and activate microglial cells [4]. A comprehensive understanding of these processes is critical for developing effective strategies to predict, prevent, and treat POD and postoperative cognitive dysfunction (POCD).

In this review, we examine studies on cytokines related to PND and explore the role of anesthesia in modulating cytokine activity. A comprehensive search was conducted of the PubMed, PubMed Central, Medline, Google Scholar, and Google databases, using the keywords, “perioperative neurocognitive disorders,” “postoperative delirium,” “postoperative cognitive dysfunction,” “neuroinflammation,” “cytokine,” and “anesthesia.”

2. What Is PND?

2.1. Definition

A recent consensus [5] has recommended the term PND to describe cognitive changes occurring during the preoperative and postoperative periods. PNDs are further classified into preexisting cognitive impairment or delirium, delirium occurring within 7 days postoperatively, cognitive decline identified within 30 days postoperatively (referred to as delayed neurocognitive recovery), and cognitive decline detected between 30 days and 12 months postoperatively (postoperative neurocognitive dysfunction).

Patients with preexisting impairment in one or more cognitive domains—including complex attention, executive function, learning, memory, language, perceptual-motor, and/or social cognition—are considered to have baseline neurocognitive dysfunction. This dysfunction can be further classified as mild (mild cognitive impairment) or major (dementia) based on the severity of impairment.

POD is characterized by acute, fluctuating changes in attention, consciousness, and cognitive function. Although it may develop preoperatively, POD most frequently occurs within 7 days following surgery. Additional features of delirium may include psychomotor disturbances (hyperactive, hypoactive, or mixed), perceptual disturbances (e.g., hallucinations or delusions), emotional changes, and sleep–wake cycle disruptions, although these are not required for diagnosis.

The term “delayed neurocognitive recovery” has replaced the traditional “early POCD” to reflect evidence that many patients recover fully from early cognitive impairments. This terminology highlights the potential for recovery. Meanwhile, “postoperative neurocognitive dysfunction” refers specifically to cognitive decline detected between 30 days and 12 months postoperatively. Beyond 12 months, the term “postoperative” is no longer applied to cognitive decline, as attributing causality to prior surgery and anesthesia becomes challenging. Generally, POCD includes both delayed neurocognitive recovery and postoperative neurocognitive dysfunction.

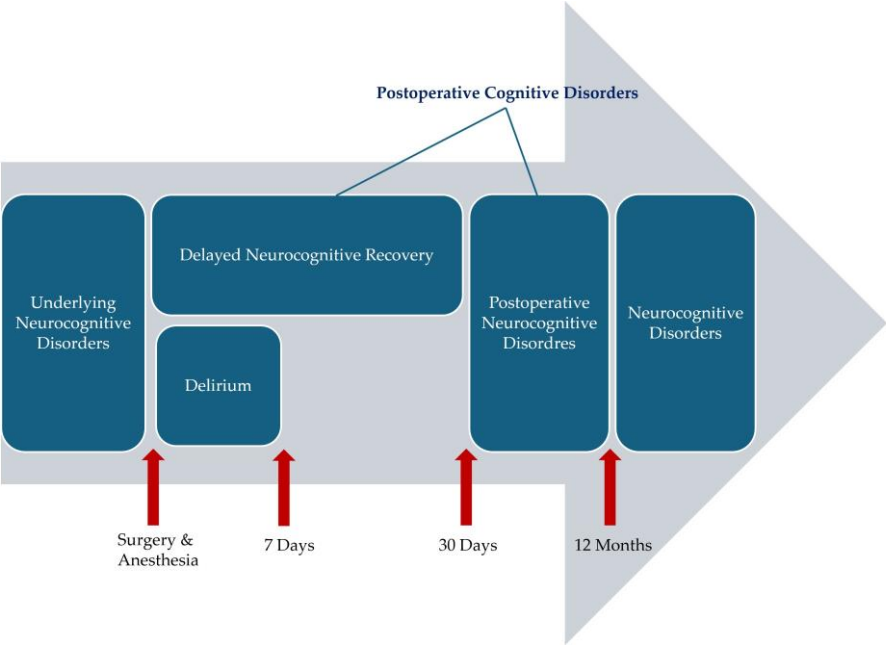


Figure 1. Definition of Postoperative Neurocognitive Disorders.

2.2. Incidence

In the general adult population, POD occurs in approximately 2.5–4.5% of cases. However, this incidence increases significantly to 12.0–23.8% among patients aged 60 years or older [6,7]. The risk of POD is influenced by the type and complexity of the surgical procedure. Data from the American College of Surgeons National Surgical Quality Improvement Program indicate that among 20,212

older patients, the incidence of POD varied by surgery type: 13.7% following cardiothoracic surgery, 13.0% after orthopedic or general surgery, 11.4% after vascular surgery, 8.0% following neurosurgery, 7.1% after plastic or otolaryngologic procedures, 6.6% following urological surgery, and 4.7% after gynecological procedures [6].

Similarly high rates of POD have been reported in other studies, including incidences of 15.3–23.4% following cardiovascular surgery [8,9], 16.9% after hip fracture surgery [10], and 22.7–26% following emergency surgery [11]. Additionally, POD was observed in 24.4% of patients admitted to the intensive care unit postoperatively [12].

The International Study of Post-Operative Cognitive Dysfunction, a landmark multicenter study, assessed cognitive decline in 1,218 elderly patients undergoing major abdominal and orthopedic surgeries. Delayed neurocognitive recovery was identified in 25.8% of patients 1 week postoperatively, while POCD was diagnosed in 9.9% of the patients 3 months postoperatively [13]. Similarly, prospective studies involving adult patients undergoing non-cardiac surgeries reported a 30% incidence of delayed neurocognitive recovery at hospital discharge and a 10–13% incidence of POCD 3 months postoperatively [14]. A systematic review of 24 studies, including 8,314 patients undergoing non-cardiac and non-neurological surgeries, estimated a pooled POCD incidence of 11.7% at 3 months postoperatively [15].

3. PND Pathogenesis

Identified risk factors for POCD include advancing age, lower education level, and a history of cerebrovascular events without residual impairment. Potential predictors of early POCD include the duration of anesthesia, postoperative infections, subsequent surgeries, and respiratory complications [14]. Risk factors for POD largely overlap with those for POCD, including advanced age, low educational level, and frailty. POD is also influenced by the type of surgery and the anesthesia method employed [16].

The exact pathogenesis of PND remains unclear. Current research has explored various contributing factors, including genetics, epigenetics, neurotransmitters, brain injury, β -amyloid protein ($A\beta$) deposition, and neuroinflammation. Recent studies in both human and animal models suggest that neuroinflammation, triggered by surgery or anesthesia, plays a significant role in PND onset and progression [16,17]. This review primarily focuses on neuroinflammation and the role of cytokines within this process.

3.1. Neuroinflammation

Inflammation is a protective response activated in reaction to external pathogens or damaged cells. For many years, the CNS was considered immunoprivileged due to the BBB, which acts as a physical barrier to prevent systemic inflammation from affecting the CNS. However, it is now increasingly recognized that the CNS is not entirely insulated from systemic inflammatory responses [18]. Similar to inflammation elsewhere in the body, neuroinflammation is a natural, protective physiological response in the brain designed to safeguard the CNS from harmful internal and external factors. While neuroinflammation serves a defensive role, excessive production of inflammatory mediators can have detrimental effects on the CNS [19].

Aseptic surgical trauma induces localized inflammation at the surgical site, which is further amplified by the release of peripheral pro-inflammatory cytokines [20,21]. These cytokines can compromise BBB integrity by upregulating cyclooxygenase-2 and matrix metalloproteinases, allowing pro-inflammatory cytokines to penetrate the CNS [21–24]. For instance, interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- α) can stimulate cyclooxygenase-2 expression in neurovascular endothelial cells, promoting prostaglandin synthesis and further disrupting the BBB [23–25]. Pro-inflammatory cytokines, such as TNF- α , IL-1 β , and IL-6, have been detected in hippocampal tissue in animal models and in human cerebrospinal fluid (CSF) following surgical trauma, indicating BBB breakdown [26–29].

Once the BBB is compromised, neuroinflammation is exacerbated by increased cytokine expression and microglial activation. Microglia, often referred to as the “resident macrophages” of the CNS, are essential for CNS maintenance, including synaptic pruning during development and synaptic scaling in neural plasticity [30]. Under normal conditions, microglia remain in an inactive state. However, inflammation and BBB disruption can activate microglia, leading to differentiation into two phenotypes: M1 (pro-inflammatory and potentially harmful) and M2 (anti-inflammatory and protective). The M1 phenotype is triggered by lipopolysaccharides (LPS) and the pro-inflammatory cytokine interferon-gamma, resulting in the production of oxidative metabolites, proteases, and cytokines, such as IL-1 β , IL-6, and TNF- α . In contrast, the M2 phenotype is activated by anti-inflammatory cytokines, such as IL-4 and IL-13, promoting tissue repair and angiogenesis through the production of arginase-1 and anti-inflammatory cytokines, including IL-10 [30–33]. These dual roles of microglia highlight their critical influence on CNS homeostasis and response to inflammation. Once activated, microglia sustain and amplify neuroinflammation by increasing the production of pro-inflammatory cytokines [30].

Several factors, including trauma, aging, dementia, hypertension, stroke, depression, diabetes, and exposure to certain drugs and toxins, are known to contribute to neuroinflammation within the CNS [30,32,33].

Memory formation occurs in the hippocampus through a process known as long-term potentiation (LTP). While the mechanisms underlying the induction and maintenance of LTP at various synapses in the CNS are complex and remain a topic of debate, LTP is generally believed to occur via high-frequency glutamatergic activation of hippocampal neurons. Pro-inflammatory cytokines can disrupt neurotransmitter signaling in the hippocampus, leading to excitotoxic neuronal damage and cognitive impairment. This vulnerability is partly attributed to the high density of cytokine receptors in the hippocampus, making it particularly sensitive to elevated pro-inflammatory cytokine levels [4].

The role of neuroinflammation has been extensively studied in neurodegenerative diseases, such as Alzheimer’s disease (AD) and Parkinson’s disease (PD), but its involvement in PND has received comparatively less attention. Research on AD and PD has demonstrated the complexity of neuroinflammatory pathways contributing to brain pathology [32–35]. The neuroinflammation hypothesis of PND suggests that patients experience an exaggerated systemic inflammatory response to surgery. In this process, macrophages at the surgical site release excessive inflammatory mediators, such as cytokines, which subsequently trigger neuroinflammation in the CNS [21].

3.2. Cytokines

To date, approximately 200 different cytokines have been identified. These small proteins exhibit a broad range of biological functions and play a crucial role in regulating host responses to infection, immune reactions, inflammation, and trauma. While some cytokines exacerbate disease through pro-inflammatory actions, others mitigate inflammation and support healing as anti-inflammatory agents. Pro-inflammatory cytokines, such as TNF- α , IL-1 β , IL-6, and IL-8, contribute to fever, inflammation, tissue damage, and, in severe cases, shock or death. In contrast, anti-inflammatory cytokines, including IL-4, IL-10, and IL-13, act as immunoregulatory molecules that modulate the pro-inflammatory response to maintain balance and prevent excessive damage [36,37]. Cytokines, particularly IL-1 β , TNF- α , and IL-6, are thought to interact with the brain via various pathways, including vagal afferents, crossing the BBB, or via the circumventricular regions. These peripheral cytokines trigger cytokine production by activated microglia, leading to a cycle of neuroinflammation.

3.3. Clinical Studies Investigating PNDs from the Perspective of Neuroinflammation and Cytokines

Several animal model studies have shown that cytokines contribute to neuroinflammation, which may lead to PNDs [28,29,38–42]. Building on these animal model studies, clinical research investigating the role of cytokines in neuroinflammation has been actively conducted over the past

decade [26,43–79]. The most extensively studied cytokines include IL-6, IL-1 β , TNF- α , high-mobility group box 1 protein (HMGB1), and S100B (Table 1).

IL-6 is a multifunctional cytokine with a profound impact on neuronal activity and a critical role in neuroinflammation. In the CNS, IL-6 is either produced and released by neurons and glial cells or transported from peripheral sources. Under normal physiological conditions, IL-6 levels in the CNS are low; however, they increase significantly in response to psychological stress, pathological conditions (such as AD and PD), or stimulation by TNF- α . IL-6 is believed to play a pathogenic role in PND by promoting neuroinflammation, which may contribute to the development and progression of these disorders [80].

Table 1. Clinical Studies on Perioperative Neurocognitive Disorders.

Study	Sample size (n)	Cohort	Study type	Surgical procedure	CSF	Plasma
Plaschke K <i>et al.</i> [81]	114	> 18	prospective, observational cohort study	open heart surgery		POST: IL-6 higher in POD
Hudetz JA <i>et al.</i> [82]	114	≥ 55	prospective, observational cohort study	open heart surgery		PRE-POST change: IL-6 higher in cognitive impairment
Li YC <i>et al.</i> [83]	37	> 60	prospective, observational cohort study	hip surgery		PRE-POST change: IL-6, S100B higher in POCD; IL- 1b, TNF-a (no significance)
Ji MH <i>et al.</i> [84]	61	65 - 85	prospective, observational cohort study	hip surgery	PRE: IL-1β higher in POCD; IL-6 (no significance)	PRE-POST change: IL-1β, IL-6 (no significance)
Liu P <i>et al.</i> [85]	338	≥ 60	prospective, observational cohort study	major noncardiac surgery		PRE-POST change: IL-6 higher in POD
Reinsfelt B <i>et al.</i> [86]	10	73 ± 6 yrs	prospective, observational cohort study	open heart surgery	PRE-POST change: IL-6, IL-8, TNF-a	

						increased accompanie d by increased AD- associated Aβ1–42
Westhoff D <i>et al.</i> [87]	61	≥ 75	RCT	hip surgery		PRE: IL- 1RA, IL-6 higher in POD; IP-10 higher in POD (no significance) ; IL-15 lower in POD (no significance)
Cape E <i>et al.</i> [43]	43	> 60	prospective, observational cohort study	hip surgery		PRE: IL-1β, IL-1RA higher in POD; IFN-γ, IGF-1 (undetected)
Capri M <i>et al.</i> [44]	74	> 65	case-control study	any kind of surgery		PRE: IL-6 higher in POD; IL-2 lower in POD

						(no significance); IL-8, IL-10 (no difference)
Kazmierski J <i>et al.</i> [45]	113		prospective, observational cohort study	open heart surgery		POST: IL-2, TNF- α increased
Lin GX <i>et al.</i> [46]	50	≥ 60	prospective, observational cohort study	major gastrointestinal surgery.		PRE-POST change: IL-6, HMGB1 higher in POCD
Vasunilashorn SM <i>et al.</i> [47]	566	≥ 70	prospective, observational cohort study	major noncardiac surgery		PRE-POST change: IL-2, IL-6 higher in POD
Skrede K <i>et al.</i> [48]	19	≥ 65	prospective, observational cohort study	hip surgery		PRE-POST change: MCP- 1 higher in POD
Zhang YH <i>et al.</i> [49]	63	≥ 65	prospective, observational cohort study	lumbar discectomy		PRE-POST change: IL-6, IL-10 higher in POCD
Neerland ET <i>et al.</i> [50]	149	≥ 60		RCT	hip surgery	PRE: sIL-6R higher in PRE: IL-6, sIL- 6R (no significance)

					POD (no significance)
Shen H <i>et al.</i> [51]	140	≥ 65	prospective, observational cohort study	open abdominal surgery	PRE: IGF-1 lower in POD; IL-6 increased (no significance)
Hirsch J <i>et al.</i> [26]	10	≥ 55	prospective, observational cohort study	major knee surgery	Delirium: PRE: MIP- 1α, MIP-1β, PRE: IFN-α2 higher in POD and IFN-α2, IL- 10 lower in POD; PRE- POST lower in change: IL-6, POCD; PRE- IL-8, IL-10, POST change: MCP-1 IFN- higher in α2, IFN-γ, IL- POD and IL- 4, IL-5, IL-12 10 higher in lower in POD POCD and IFN-α2, IL-12, and IL- 4 lower in POCD

Kline R <i>et al.</i> [52]	30	≥ 65	prospective, observational cohort study	major noncardiac surgery	PRE-POST change: IL-6, IL-8, TNF-α higher in cognitive decline; IL-10 (no significance)
Sun L <i>et al.</i> [53]	112	65-85	prospective, observational cohort study	oral cancer free flap surgery	PRE-POST change: IL-6 higher in POD
Jiang J <i>et al.</i> [54]	44	≥60	prospective, observational cohort study	head and neck cancer	PRE: IGF-1 lower in POCD; PRE-POST change: TNF-α higher, IGF-1 lower in POCD
Yu H <i>et al.</i> [55]	51	18-65	prospective, observational cohort study	cytoreductive surgery and hyperthermic intraperitoneal chemotherapy	PRE-POST change: IL-6, HMGB1,S100 B higher in POCD; TNF-α (no significance)
Guo HY [56]	51	60-82	prospective, observational cohort study	open heart surgery	POST: IL-1β, IL-6, MMP-3,

					MMP-9 higher in POCD
Sajjad MU <i>et al.</i> [57]	331	≥ 65	prospective, observational cohort study	hip surgery	PRE: IL-8 higher in POCD; TNF- α, IL-1β (undetected)
Chen Y <i>et al.</i> [58]	266	≥ 18	prospective, observational cohort study	open heart surgery	PRE-POST change: IL-6 higher in POD
Lin X <i>et al.</i> [59]	447	≥ 65	prospective, observational cohort study	hip/knee surgery	PRE: IL-6, TNF-α higher in POD PRE-POST change: IL-6, TNF-α higher in POD
Yuan Y <i>et al.</i> [60]	34	≥ 65	prospective observational case-control preliminary study	hip surgery	PRE-POST change: IL-6 higher in POD; IL-1β, TNF-α (no significance)
Danielson M <i>et al.</i> [61]	27	65-76	prospective, observational cohort study	hip/knee surgery	PRE-POST change: IL-6, IL-8 higher in POCD (transiently increased)

					CSF/serum albumin ratio & CSF, serumS100B)
Casey CP <i>et al.</i> [62]	114		prospective, observational cohort study	major noncardiac surgery	PRE-POST change: IL-8 higher in POD (in relation with severity); IL-1β, IL-1RA, IL-2, IL-4, IL- 6, IL-10, IL- 12p70, MCP- 1, TNF-α (no significance)
Kavrut Ozturk N <i>et al.</i> [63]	82	> 50	prospective, observational cohort study	Robotic-Assisted Laparoscopic Radical Prostatectomy	PRE-POST change: S100B higher in POCD
Ballweg T <i>et al.</i> [64]	110		prospective, observational cohort study	open thoracoabdomina l aortic aneurysm /TEVAR	PRE-POST change: IL-8, IL-10 higher in POD; IL-1β, IL-1RA, IL-2

							(no significance)
CheheiliSobbi S <i>et al.</i> [65]	89	≥ 50	prospective, observational cohort study	open surgery	heart		PRE-POST change (ex vivo- stimulated production): TNF- α , IL-6, IL-10 higher in POD (no significance)
Lv XC <i>et al.</i> [66]	221	> 18	retrospective study	open surgery	heart		PRE-POST change: IL-6 higher in POD
Zhang S <i>et al.</i> [67]	390	> 18	prospective, observational cohort study	open surgery	heart		PRE-POST change: IL-6 higher in POD
Taylor J <i>et al.</i> [68]	72	≥ 65 yrs	prospective, observational cohort study	non-intracranial surgery		IL-6 correlates with S100B	PRE-POST change: S100B higher in POD
Wu JG <i>et al.</i> [69]	64	≥ 21 yrs	prospective, observational cohort study	non-intracranial surgery		PRE-POST change: IL- 18 (no significance)	PRE-POST change: IL-18 (no significance)

Khan SH <i>et al.</i> [70]	71	≥ 18 yrs	secondary analysis of blood samples from a RCT	esophagectomy	PRE-POST change: IL-8, IL-10 higher in POD; S100B increase and IGF-1 (correlated with greater POD severity)
Oren RL <i>et al.</i> [71]	76	45–60 or ≥ 70 yrs	prospective observational study	spine surgery	PRE-POST change: IL-8, IL-6 higher in POD
Zhang Y <i>et al.</i> [72]	126	≥60 yrs	prospective, observational cohort study	hip/knee surgery	PRE-POST change: IL-6, sIL-6R higher in POD; IL-1β, IL-2, IL-4, IL- 10, TNF-α (no significance)
Su LJ <i>et al.</i> [73]	318	≥ 18 yrs	prospective, observational cohort study	open heart surgery	Post: IL-6, TNF-α, sTNFR-1, sTNFR-2 higher in POD; IL-1β

						(no significance)
Imai T <i>et al.</i> [74]	221	24–88 yrs	retrospective study	head and neck cancer		POST: IL-6 higher in POD
Taylor J <i>et al.</i> [75]	170	≥ 65 yrs	prospective, observational cohort study	non-intracranial surgery		POST: IL-6 higher in cognitive decline
Ruhnau J <i>et al.</i> [76]	44	≥60 yrs	prospective, observational cohort study	spine surgery		PRE-POST change: S100B, IL-6, IL-1β increased in POD
Lozano-Vicario L <i>et al.</i> [77]	60	≥ 75 yrs	prospective, observational cohort study	hip surgery	PRE: CXCL9 lower in POD	PRE: CXCL9 lower in POD
Zhang S <i>et al.</i> [78]	212	≥ 18 yrs	prospective, observational cohort study	open heart surgery		POST: IL-6 higher in POCD
Ko H <i>et al.</i> [79]	43	> 30 yrs	prospective, observational cohort study	open heart surgery		PRE: TNF-α lower in POD; IL-6 higher (No significance), IL-1β (no difference)

CSF, cerebrospinal fluid; CXCL 9, C-X-C motif chemokine ligand 9; HMGB1, high-mobility group box 1 protein; IGF-1, insulin-like growth factor-1 IL, interleukin; IL-1RA, interleukin-1 receptor antagonist; IP-10, interferon gamma-induced protein 10; IFN- γ , interferon gamma; MCP-1, monocyte chemoattractant protein-1; MIP-1 α , macrophage inflammatory protein-1 alpha; S100B, S100 calcium binding protein B; sIL-6R, soluble interleukin-6 receptors; sTNFR, soluble tumor necrosis factor receptors; TNF- α , tumor necrosis factor alpha; PRE, preoperative; POST, postoperative; PRE-POST change, preoperative-postoperative difference; POCD, postoperative cognitive dysfunctions; POD, postoperative delirium; RCT, randomized controlled trial.

IL-1 β is a versatile pro-inflammatory cytokine that plays a central role in coordinating inflammatory and host defense responses in peripheral tissues. In the healthy adult brain, IL-1 β is expressed at low levels. However, following localized brain injury or insult, its expression is significantly upregulated by microglia [88].

TNF- α , another pro-inflammatory cytokine, is primarily produced by neurons and glial cells, including astrocytes and microglia, which are the predominant glial cell types. TNF- α plays a crucial role in regulating acute-phase inflammation by initiating signaling cascades of inflammatory cytokines, making it a central mediator of the inflammatory response [89].

HMGB1 proteins are part of the damage-associated molecular pattern family. These highly conserved non-histone nuclear proteins play a crucial role in maintaining chromatin DNA structure. HMGB1 is involved in driving pathogenic inflammatory responses and has been implicated in a variety of conditions, including epilepsy, septic shock, ischemia, PD, and AD [58]. When receptors of IL-1 β and TNF- α are excessively activated, they downregulate metabotropic glutamate receptors, which enhances AMPA/NMDA signaling and disrupts LTP. Additionally, HMGB1 can amplify glutamate signaling through NMDA receptors, increasing the influx of glutamate into hippocampal neurons and ultimately causing glutamate toxicity. TNF- α further exacerbates this issue by suppressing inhibitory neurotransmission through the downregulation of GABA receptors, disrupting the balance between excitatory and inhibitory signaling and promoting glutamate toxicity. This harmful cycle is intensified by T-cell-mediated glutamate release from activated microglia via a distinct glutamate transporter subtype. Together, these mechanisms contribute to glutamate toxicity in the hippocampus, leading to neuronal death and cognitive dysfunction [4,91].

Research into the relationship between plasma or serum cytokine levels and PND has yielded inconclusive results. Chen et al. [58] reported that IL-6 levels significantly increased postoperatively compared to preoperative levels in patients who developed POD following cardiac surgery. Similarly, Lin et al. [59] observed a significant postoperative increase in IL-6 levels in patients with POD in a study of 447 individuals undergoing knee or hip surgery. In contrast, Cheheili-Sobbi et al. [65] found no significant postoperative increase in IL-6 levels in patients with POD after cardiac surgery. Additionally, Casey et al. [62] reported no significant correlation between IL-6 levels and the occurrence of POD before and after non-cardiac surgery. Similarly, Kline et al. [52] observed an increase in TNF- α levels postoperatively compared to preoperative levels in patients who developed POD. However, Yu et al. [55] found that this change was not statistically significant. The authors suggested that these inconsistencies could be attributed to variations in cytokine analysis methods, the timing of sample collection, differences in patient group composition, or the combination of prevalent and incident delirium cases in some studies.

Examining cytokines in CSF rather than serum or plasma offers a more rational approach when studying PNDs. Since CSF is in direct contact with the brain's extracellular fluid, it provides a more accurate indicator of central biochemical changes compared to peripheral blood markers. Several cytokines have been found to be increased in the CSF following surgery, with IL-6 and IL-8 showing more significant elevations in the CSF compared to serum [43,50,57,59,61,86,92,93]. These findings suggest that the interactions between peripheral and central cytokines could reflect impaired BBB function, a potential mechanism underlying PNDs. Studies by Ji et al. [84], Neerland et al. [50], and Lin et al. [59] have demonstrated consistent changes in cytokine levels between CSF and plasma, supporting the hypothesis that PND is caused by neuroinflammation resulting from BBB disruption.

S100B, also known as S100 calcium-binding protein B, is primarily produced by astrocytes in brain tissue. Elevated serum or urine levels of S100B are often interpreted as being a result of increased CSF levels, which may arise due to astroglial activation or disruption of the BBB [94]. Taylor et al. [68] conducted a study to investigate neuroinflammation caused by BBB disruption as a mechanism underlying POD. That study, conducted on 72 patients aged 65 years and older who underwent non-intracranial surgery, demonstrated that changes in S100B, a plasma biomarker of astrocytic injury/activation, were associated with the incidence and severity of delirium. Importantly, these changes were consistent with alterations in CSF IL-6 levels. Several studies have also shown

elevated S100B levels in the blood of PND patients, indicating a close relationship between PND, BBB disruption, and neuroinflammation [55,63,70,76,83].

4. Influence of Anesthesia on PND

Growing evidence suggests that PND arises from the combined effects of surgical procedures and anesthesia. Although some studies have indicated that anesthesia alone may not directly cause cognitive changes, anesthetic agents have been shown to influence glial cell phenotypes and modulate their activation, potentially leading to either beneficial or harmful effects on the CNS [95].

Neuroinflammatory responses caused by surgical insult are unavoidable for patients, particularly as the aging population grows. PND has emerged as a significant postoperative complication, prompting ongoing efforts to mitigate its occurrence. The relationship between the use of specific anesthetic agents and PND has been widely studied, though the findings are sometimes inconsistent. Generally, it is estimated that the shorter the duration of action of an anesthetic agent, the shorter the duration of POCD in the immediate postoperative period [96]. Various studies have investigated the impact of anesthetic methods on PND through different approaches. Table 2 summarizes research that has identified how anesthetic methods influence PND by affecting neuroinflammation mechanisms through cytokine modulation.

4.1. Impact of Anesthetic Method on PND from the Perspective of Neuroinflammation and Cytokines

The most common general anesthetics include halothane-based inhalation agents and intravenous agents, with propofol being the most widely used. However, the impact of intravenous and volatile anesthetics on PND in humans remains uncertain. While numerous studies have explored this topic, many have been limited by small sample sizes, suboptimal diagnostic methodologies, or an insufficient focus on this specific question.

Table 2. Clinical Studies on Perioperative Neurocognitive disorders and Anesthetic Methods.

Study	Sample size (n)	Cohort (yrs)	Study type	Surgical procedure	Anesthetic exposure	Key findings
Lili X <i>et al.</i> [97]	40	> 65	RCT	elective abdominal surgery	UTI vs control	lower incidence of POCD in the UTI group; S100B, IL-6 decreased in the UTI group
Jildenstål PK <i>et al.</i> [98]	450		RCT	elective eye surgery	AAI vs control	IL-6 lower in the AAI group; IL-6 higher in patients with a MMSE < 25
Li Y <i>et al.</i> [99]	120	> 60	RCT	laparoscopic cholecystectomy	DEX vs control	IL-1β, IL-6 lower in the DEX group; IL-1β, IL-6 higher in patients who developed POCD on day 1 following surgery
Jia Y <i>et al.</i> [100]	240	≥70	RCT	open colorectal surgery	fast-track surgery vs traditional	POD occurrence lower in the fast-track surgery group; IL-6 decreased in fast-track surgery group
Chen K <i>et al.</i> [101]	87	> 65	RCT	spine surgery	lidocaine vs control	MMSE scores markedly higher in the lidocaine group; S100B, IL-6 decreased in the lidocaine group
Qiao Y <i>et al.</i> [102]	90	65-75	RCT	resection of an esophageal carcinoma	Sevo vs Sevo-PRE methylprednisolone vs IV propofol	MMSE, MoCA scores lower in the Sevo group; TNF-α, IL-6, S100B higher in the Sevo group > IV propofol group > Sevo + PRE methylprednisolone
Chen W <i>et al.</i> [103]	148	61-89	retrospective study,		DEX vs control	incidence of POCD lower in the Dex group; IL-6, TNF-α lower in the Dex group

Wang KY <i>et al.</i> [104]	80	≥ 60	RCT	radical resection for esophageal cancer under one lung ventilation	UTI vs control	incidence of POCD lower in the UTI group; S100B, IL-6 lower, IL-10 higher in the UTI group
Xin X <i>et al.</i> [105]	120	> 65	RCT	hip arthroplasty	PRE hypertonic saline vs normal saline	lower risk of POD in the PRE hypertonic group; higher TNF- α associated with POD, IL-1 β , IL-6, IL-10, S100B not significantly related to POD
He Z <i>et al.</i> [106]	90	65-75	RCT	laparotomy colon carcinoma surgery	ischemic preconditioning vs control	MoCA scores higher in the ischemic preconditioning group; IL- 1 β , TNF- α , S100B lower in the remote ischemic preconditioning group
Lu XY <i>et al.</i> [107]	70		RCT	radical surgery for cervical cancer	remifentanil vs fentanyl	POCD occurrence lower in the remifentanil group; IL-6, TNF- α lower in the remifentanil group
Zhang H <i>et al.</i> [108]	120	65-75	RCT	esophageal carcinoma resection	midazolam + propofol vs midazolam + Sevo vs DEX + propofol vs DEX+ Sevo	MMSE and MoCA scores lower in the midazolam + Sevo (vs midazolam + propofol), MMSE and MoCA scores higher in the DEX + Sevo (vs midazolam); IL-6, TNF- α , S100B higher in the midazolam + Sevo (vs midazolam + propofol), IL-6, TNF- α , S100B lower in the DEX + Sevo (vs midazolam); POCD incidence higher in Sevo anesthesia and DEXv could alleviate POCD

Lee C <i>et al.</i> [109]	354	> 65	RCT	laparoscopic major non-cardiac surgery	intraoperative DEX infusion vs intraoperative DEX bolus vs control	POCD incidence and duration lower in DEX infusion, POCD duration lower in DEX bolus (vs control); IL-6 lower in DEX groups
Quan C <i>et al.</i> [110]	120	≥ 60	RCT	abdominal surgery	Deep (BIS target 30–45) vs Light (BIS target 45-60)	POCD incidence lower in the Deep group (at 7 days after surgery); IL-1β lower in the Deep group, IL-10, S100B no significance
Kim JA <i>et al.</i> [111]	143	18-75	RCT	thoracoscopic lung resection	DEX-Sevo vs Sevo	emergence agitation lower in Dex-Sevo group, POD no difference; IL-8, IL-10 lower & IL6/IL10 ratio, IL8/IL10 ratio in Dex-Sevo group, IL-6 no significance
Wang Y <i>et al.</i> [112]	100	20–60	RCT	thoracotomy for esophageal cancer	intercostal nerve block vs control	MMSE score higher in the intercostal nerve block group; IL-6, TNF-α lower, IL-10 higher in the intercostal nerve block group
Hassan WF <i>et al.</i> [113]	80		RCT	laparoscopic cholecystectomy	magnesium sulphate vs control	POST S100B higher in the control group (vs PRE), no difference in the magnesium sulphate group
Xin X <i>et al.</i> [114]	60	> 65	RCT	laparoscopic cholecystectomy	DEX vs control	POD incidence lower in DEX group; TNF-α lower, IL-10 higher in Dex group

Mei B <i>et al.</i> [115]	366	≥ 65	RCT	total knee arthroplasty	spinal anesthesia supplemented with propofol vs Dex	POD incidence lower in DEX group; S100B higher in the propofol group, TNF-α lower, IL-6 no difference
Uysal Aİ <i>et al.</i> [116]	114	> 65	RCT	trochanteric femur fracture surgery	spinal anesthesia supplemented with paracetamol vs femoral nerve block	POD incidence lower in the femoral nerve block group; IL-8 lower in the femoral nerve block group, IL-6 no significance
Wang J <i>et al.</i> [117]	71	≥ 65	RCT	Prone Spinal Surgery	lung-protective ventilation vs conventional mechanical ventilation	POD incidence lower in the lung protective ventilation group; IL-6 lower, IL-10 higher in the lung protective ventilation group
Hu J <i>et al.</i> [118]	177	60-80	RCT	transthoracic oesophagectomy	TIVA vs TIVA-DEX	POD incidence, emergence agitation lower in TIVA-DEX group; IL-6 lower TIVA-DEX group
Oh CS <i>et al.</i> [119]	82	> 50	RCT	total hip replacement	moderate vs deep NMB	POD no difference; IL-6 lower in the deep NMB group

Jiang P <i>et al.</i> [120]	142	18-80	RCT	esophagectomy	general anesthesia vs general anesthesia combined with epidural anesthesia	MoCA score higher in the general anesthesia combined with epidural anesthesia group; IL-6, IL-8, TNF- α lower in the general anesthesia combined with epidural anesthesia group
Li Y <i>et al.</i> [121]	544	≥ 60	RCT	laparoscopic abdominal surgery	Sevo vs propofol	POCD no difference; associated with an increased likelihood of delayed neurocognitive recovery; IL-6 higher in POCD
Zhang Z <i>et al.</i> [122]	174	18–79	RCT		DEX vs control	POCD incidence lower in DEX group; TNF- α , IL-6 lower in Dex group
Huang Q <i>et al.</i> [123]	90	≥ 60	RCT	laparoscopic radical gastrointestinal tumor resections	insulin (20 U/0.5 mL insulin administered intranasally) vs control	POD incidence lower in the insulin group; TNF- α , IL-6, IL-1 β lower in the insulin group
Feng T <i>et al.</i> [124]	60	18–80	RCT	total hip arthroplasty	inside approach of the fascia iliaca compartment block (FICB) vs outside approach of the FICB	POCD incidence lower in the inside approach group; IL-1b, IL-6 lower in the inside approach group

Chen S <i>et al.</i> [125]	103	> 65	RCT	cardiac surgery	transversus thoracis muscle plane (TTMP) block vs control	POCD lower in TTMP block group; IL-6,TNF- α ,S-100 β lower in TTMP block group
Wang W <i>et al.</i> [126]	100	60-85	RCT		DEX vs control	MMSE and MoCA scores higher in Dex group; IL-6,TNF- α ,S-100B lower in Dex group
Wang JY <i>et al.</i> [127]	159	65-85	RCT	thoroscopic lobectomy	goal-directed therapy vs conventional	POD incidence lower in the goal-directed therapy group; IL-1 β , IL-6, TNF- α , S-100B lower in the goal-directed therapy group
Tang Y <i>et al.</i> [128]	120	60-80	RCT	hepatic lobectomy	0.3 μ g, 0.6 μ g/kg/hr DEX vs control	POD & POCD incidence lower in 0.3 μ g, 0.6 μ g/kg/hr DEX group; TNF- α , IL-1 β lower, IL-10 higher in 0.3 μ g, 0.6 μ g/kg/hr Dex group
Xiang XB <i>et al.</i> [129]	168	65-80	RCT	laparoscopic gastrointestinal surgery	methylprednisolone vs control	POD incidence lower in the methylprednisolone group; TNF- α loer in the methylprednisolone group; methylprednisolone does not reduce the severity of POD
Kurup MT <i>et al.</i> [130]	64	60-80	RCT	open abdominal surgery	DEX vs lidocaine	TNF- α , IL-6, S100B levels (no significance), IL-1 decreased in Dex (vs lidocaine), POCD no significance
Lai Y <i>et al.</i> [131]	90	> 65	RCT	thoroscopic lobectomy or segmentectomy	DEX vs lidocaine vs control	POD incidence no significance; IL-6, TNF- α lower in Dex and lidocaine

Xu F <i>et al.</i> [132]	84	≥ 60	RCT	shoulder arthroscopy	PRE hypertonic saline vs normal saline	POD lower in the PRE hypertonic saline group; IL-6, TNF-α lower in the PRE hypertonic saline group
Han C <i>et al.</i> [133]	84	≥ 60	RCT	gastrointestinal surgery	esketamine vs control	incidence of delayed neurocognitive recovery lower in the esketamine group, no difference in POCD at 3 months after surgery; IL-6 and S100B lower in the esketamine group
Zhu M <i>et al.</i> [134]	60	> 65	RCT	hip surgery	quadratus lumborum block vs control	POCD incidence lower in the quadratus lumborum block group; HMGB1, IL-6 lower in the quadratus lumborum block group
Zhi Y <i>et al.</i> [135]	140	60-85	RCT		TIVA vs TIVA-etomidate	MMSE, MoCA scores higher in TIVA-etomidate group; IL-6, S100B lower, IL-10 higher in TIVA-etomidate group
Mi Y <i>et al.</i> [136]	116	≥ 60	RCT	noncardiac surgery	insulin (40 U/1 mL administered intranasally) vs control	POCD incidence lower in the insulin group; TNF-α lower in the insulin group
Sun M <i>et al.</i> [137]	140		RCT	orthopaedic surgery or pancreatic surgery	insulin (40 IU/400 µL administered intranasally) vs control	MMSE and MoCA-B scores higher, POD incidence lower in the insulin group; IL-6, S100B lower in the insulin group
Fu W <i>et al.</i> [138]	132	60-80	RCT	ureteroscopic holmium laser lithotripsy	etomidate-remifentanil-DEX vs control	MMSE scores higher in the etomidate-remifentanil-DEX group; S100B lower in the etomidate-remifentanil-Dex group

Luo T <i>et al.</i> [139]	129		RCT	non-cardiac thoracic surgery	0.2, 0.5 mg/kg esketamine vs control	MMSE scores no difference; IL-6, S100B lower in the esketamine groups
Hsiung PY <i>et al.</i> [140]	110	> 20	RCT	thoracoscopic tumor resection	nonintubated vs intubated	Qmci-TW higher in the nonintubated group; IL-6 lower in the nonintubated group
Yin WY <i>et al.</i> [141]	94	60-85	retrospective study,	orthopedic surgery	paracoxib vs control	MoCA score higher in the paracoxib group; TNF- α , IL-6, IL-1 β lower, IL-10, MCP-1 higher in the paracoxib group
Huo QF <i>et al.</i> [142]	397	65-80	RCT	Total hip arthroplasty	DEX vs UTI vs DEX-UTI	POCD incidence lower in DEX-UTI group; IL-6 lower in Dex-UTI group
Hindman BJ <i>et al.</i> [143]	76	> 65	RCT	posterior lumbar fusion	tranexamic acid vs control	POD incidence no difference; TNF- α lower in the tranexamic acid group, IL-10, IL-6, S100B no significance
Ye C <i>et al.</i> [144]	218	65-90	RCT	thoracolumbar compression fracture surgery	DEX vs control	POD incidence lower in DEX group; IL-6, TNF- α lower in DEX group, IL-1 no significance
Ma X <i>et al.</i> [145]	108	18–70	RCT	resection of gastrointestinal tumor resection	narcotrend vs physician experience	POCD incidence lower in the narcotrend group; IL-1 β , TNF- α lower in the narcotrend group

AAI, auditory evoked potential index; BIS, bispectral index; CSF, cerebrospinal fluid; DEX, dexmedetomidine; IL, interleukin; IFN- γ , interferon gamma; MCP-1, monocyte chemoattractant protein-1; NMB, neuromuscular blockade; MMSE, mini-mental state exam; MoCA, montreal cognitive assessment; S100B, S100 calcium binding protein B; Sevo, sevoflurane; TNF- α , tumor necrosis factor alpha; PRE, preoperative; POST, postoperative; PRE-POST change, preoperative-postoperative difference; POCD, postoperative cognitive dysfunctions; POD, postoperative delirium; RCT, randomized controlled trial; UTI, ulinastatin; Qmci-TW, Taiwan version of quick mild cognitive impairment screen.

Li et al. [121] conducted a randomized controlled study on 544 patients aged 60 years and older undergoing laparoscopic abdominal surgery to compare the effects of sevoflurane and propofol on POCD. The study revealed no significant difference in the incidence of delayed neurocognitive recovery between patients receiving propofol-based anesthesia and those receiving sevoflurane-based anesthesia. This suggested that the choice of anesthetic may not be a modifiable factor for preventing delayed neurocognitive recovery. However, the study identified elevated serum IL-6 levels as an independent risk factor for delayed neurocognitive recovery, providing clinical evidence of inflammation's role in its development.

In another study, Qiao et al. [102] examined 90 patients aged 65–75 years undergoing esophageal cancer surgery to assess the incidence of POCD and changes in cytokine levels. Patients were anesthetized with sevoflurane, propofol, or sevoflurane, along with pre-treatment with methylprednisolone. The study found a higher incidence of POCD in patients receiving sevoflurane anesthesia compared to those on a propofol regimen. Methylprednisolone pre-treatment reduced the incidence of POCD in elderly patients undergoing sevoflurane anesthesia. The authors concluded that methylprednisolone could mitigate POCD by suppressing IL-6 and TNF- α levels.

Studies have also compared regional anesthesia (RA) with general anesthesia, or RA combined with general anesthesia (via inhalation or intravenous agents), as well as different RA techniques [116,120,124,125,134]. Local anesthetics, a cornerstone of RA, possess anti-inflammatory properties. These include interrupting nociceptive transmission to reduce neurogenic inflammation and exerting intrinsic anti-inflammatory effects independent of sodium channel blockade, acting directly on immune cells. Unlike immunosuppressive drugs, local anesthetics modulate excessive inflammatory responses without compromising the body's natural defenses. RA's modulation of perioperative inflammation is also linked to its opioid-sparing effect, which reduces exposure to opioids, known for both their immunosuppressive and pro-inflammatory properties [146].

Jiang et al. [120] investigated 142 patients aged 18–80 years undergoing esophageal cancer surgery with or without the addition of epidural block to general anesthesia. They demonstrated that combining general and epidural anesthesia reduced the incidence of POCD by mitigating the inflammatory response.

Among RA-related studies, the findings of Feng et al. [124] are particularly noteworthy. They evaluated the effects of different fascia iliaca compartment block (FICB) approaches on postoperative outcomes, including POCD, in 60 patients aged 18–80 years undergoing total hip arthroplasty under general anesthesia with sevoflurane. The FICB was performed using two methods: the “inside” and “outside” approaches. The inside FICB approach provided superior anesthetic effects, improved postoperative analgesia, reduced reliance on postoperative analgesics, and resulted in a lower incidence of POCD. The higher levels of IL-1 β and IL-6 observed in the outside approach were identified as factors contributing to the increased POCD incidence in this group.

4.2. Impact of Dexmedetomidine on PND from the Perspective of Neuroinflammation and Cytokines

A recent meta-analysis indicated that the use of midazolam, propofol, desflurane, and sevoflurane is associated with a higher incidence of delirium compared to dexmedetomidine (DEX). DEX, an $\alpha 2$ adrenoceptor agonist, was first approved for clinical use by the FDA in 1999, primarily for sedation. In animal models of systemic inflammatory responses and surgical injury, DEX has demonstrated the ability to mitigate neuroinflammation and neuroapoptosis. A literature review indicated that DEX exerts its neuroprotective effects primarily through the upregulation of $\alpha 2$ adrenoceptors. Preclinical studies have indicated that DEX significantly reduces neuroinflammation and neurodegeneration following neurological injury by decreasing hippocampal expression of IL-1 β , IL-6, and TNF- α , as well as reducing the activation of astrocytes and microglia. DEX improves neuroinflammatory responses by inhibiting inflammatory mediators, regulating apoptotic signaling pathways, and reducing the production of oxygen-free radicals [147,148].

In an early study on DEX, Li Y et al. [99] demonstrated that its combined use with propofol-based general anesthesia reduced the incidence of POCD. This effect was attributed to a reduction in the inflammatory response, as evidenced by decreased levels of IL-1 β and IL-6. Similarly, a recent study by Ye C et al. [144] reported that the combined use of DEX and propofol-based general anesthesia decreased the incidence of POD. Additionally, they observed reduced IL-6 and TNF- α levels, concluding that these reductions indicate that a neuroinflammatory response is the underlying mechanism. Meanwhile, Kim JA et al. [111] conducted a study involving 143 patients undergoing thoroscopic lung resection surgery to investigate the effects of adding DEX to sevoflurane anesthesia on emergence agitation and POD. They reported that while DEX reduced emergence agitation, it did not decrease the incidence of POD. Additionally, they observed higher IL-6/IL-10 and IL-8/IL-10 ratios in the group receiving DEX, indicating a pro-inflammatory cytokine balance in DEX group. Furthermore, norepinephrine and epinephrine levels were lower in the DEX group, leading them to conclude that the reduction in emergence agitation was due to the effect of catecholamines rather than anti-inflammatory action.

Several studies have explored the effects of DEX administration methods and dosage on PND. Lee C et al. [109] investigated the relationship between the timing and dosage of DEX administration and POD incidence. They found that preoperative, prophylactic continuous infusion of DEX significantly reduced the incidence of POD in elderly patients for up to 5 days following laparoscopic major non-cardiac surgery. Furthermore, prophylactic DEX infusion, regardless of timing or dosage, decreased the duration of POD. Regarding inflammatory cytokines, their study showed that IL-6 levels were significantly lower in patients who received higher doses of DEX with bolus and continuous infusion during surgery compared to those who received lower doses via bolus injection at the end of surgery, correlating with a lower incidence of POD.

Tang Y et al. [128] examined the effect of DEX dosage on PND in elderly patients undergoing hepatic lobectomy. They concluded that an intraoperative DEX infusion at a dose of 0.3 or 0.6 $\mu\text{g/kg/hr}$ reduces the incidence of POCD and POD. This protective mechanism likely involves the downregulation of TNF- α and IL-1 β and the upregulation of IL-10 expression, restoring the balance between pro-inflammatory and anti-inflammatory responses.

4.3. Potential Therapeutic Approaches Targeting Cytokines

Various studies have explored the relationship between anesthesia and PND from the perspectives of neuroinflammation and cytokines. Research on the depth of anesthesia has shown that adjusting the depth using anesthesia depth monitoring equipment [98,145] and maintaining deeper anesthesia [94] can reduce the incidence of POCD. Deeper levels of anesthesia were consistently associated with decreased POCD occurrence.

Studies investigating the effect of ulinastatin (UTI) administration on PND have also been reported [104,142,149]. UTI, derived from human urine, is known to inhibit enzyme activity, stabilize lysosomal membranes, and effectively reduce systemic inflammatory responses. It achieves this by directly suppressing the activation of neutrophils and monocyte-macrophages, as well as by capturing LPS and binding to LPS receptors, thereby inhibiting LPS-induced systemic inflammatory responses. UTI has been shown to reduce the incidence of POCD and lower the levels of IL-6 and S100B compared to controls, indicating that UTI alleviates neuroinflammatory responses.

Remote ischemic preconditioning, a method involving repeated temporary restriction of blood flow to a limb, has demonstrated promising neuroprotective effects. Studies in rats have demonstrated that remote ischemic preconditioning protects against cerebral ischemia by modulating peripheral immune responses [148]. However, clinical trials on this technique are limited. He Z et al. [106] investigated the effects of ischemic preconditioning on cognitive function in 90 patients aged 65–75 years undergoing laparoscopic colorectal cancer surgery. They found that remote ischemic preconditioning improved early postoperative cognitive function and reduced the serum levels of S100B, IL-1 β , and TNF- α . These improvements in cognitive function were attributed to the inhibition of the inflammatory response triggered by surgery. This method offers a non-

pharmacological approach with significant potential for clinical application as a less invasive alternative to cerebral preconditioning.

5. Future Directions

The findings summarized in Table 2 generally demonstrate consistent results. Intravenous anesthesia with propofol, the combination of RA with general anesthesia, and the administration of DEX or UTI were found to reduce the incidence of PNDs. However, despite ongoing research into various anesthetic agents and methods aimed at mitigating neuroinflammatory responses and reducing PND, no definitive conclusions have been reached. This is largely due to the limited number of studies available for meta-analysis and the considerable variability across studies in terms of patient age, types of surgeries, and anesthetic techniques used.

The studies summarized in Table 2 demonstrate inconsistencies, particularly in cytokine-related outcomes, which vary across investigations. Nevertheless, clinical outcomes associated with PND, specifically involving intravenous anesthesia with propofol, the combination of regional anesthesia and general anesthesia, as well as the administration of dexmedetomidine (DEX) or ulinastatin (UTI), consistently suggest a potential for these approaches to reduce the incidence of PND. Additional preclinical studies and well-designed clinical trials are required to further elucidate the precise mechanisms linking surgery, neuroinflammation, and the development of neurological disorders. Furthermore, research should focus on evaluating the efficacy and safety of therapeutic agents aimed at mitigating these post-surgical complications.

To address these challenges, the authors recommend that large-scale multicenter studies be conducted. These studies should include a homogeneous participant group, ideally with a unified age range, standardized surgical procedures, and consistent anesthetic methods to enhance the comparability and reliability of the results.

6. Conclusions

In conclusion, the exact pathogenesis of PND remains unclear. Recent human and animal models have indicated that neuroinflammation triggered by surgery or anesthesia plays a significant role in PND onset and progression. The inflammatory response induced by surgery and anesthesia has been shown to compromise BBB integrity, leading to proinflammatory cytokine infiltration, microglia activation, and the induction of neuroinflammatory responses. These processes ultimately contribute to the development of PND. Several studies have sought to reduce PND by modifying anesthetic agents and techniques. Unfortunately, the evidence supporting these interventions remains limited. Therefore, further research involving a standardized participant age group, consistent surgical procedures, and uniform anesthetic methods is required to achieve more reliable conclusions and identify effective strategies for mitigating PND.

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