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The Effect of Dexmedetomidine on Post-Operative C-Reactive Protein Levels in Patients Undergoing Brain Tumor Resection: A Literature Review

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ABSTRACT

Background: Brain tumour resection surgery is a major intracranial procedure that triggers systemic stress and inflammatory responses, characterized by an increase in C-reactive protein (CRP) levels postoperatively. Dexmedetomidine, a selective α₂-adrenergic receptor agonist, has been reported to have sympatholytic and anti-inflammatory effects that potentially reduce inflammatory markers, including CRP. Objective: To review the scientific evidence regarding the effect of dexmedetomidine administration on postoperative CRP levels in patients undergoing brain tumor resection. Methods: A literature review was conducted by examining pharmacological and physiological evidence, as well as clinical data from studies on neurosurgical populations and other relevant types of surgery. The literature covered the mechanism of action of dexmedetomidine, postoperative CRP dynamics, and studies assessing the anti-inflammatory effects of dexmedetomidine. Results: CRP generally peaked on day 2 postoperatively and decreased on day 4 in patients without infection, whereas in patients with complications, CRP values remained high or increased again on day 5. Several clinical studies in cardiac and spinal surgery have shown that dexmedetomidine can reduce CRP, IL-6, TNF-α, and other inflammatory mediators. In the sepsis population, dexmedetomidine also reduced CRP compared to controls. Although direct data in the brain tumor resection population are still limited, its pharmacological effects consistently support its potential for inflammatory modulation. Conclusion: Dexmedetomidine has the potential to reduce the postoperative inflammatory response through suppression of sympathetic activity and cytokine modulation, which may indirectly reduce elevated CRP in patients after brain tumor resection. More specific clinical research in neurosurgical populations is needed to confirm its efficacy and clinical implications for preventing complications and improving neurological outcomes.

KEYWORDS: Dexmedetomidine, C-reactive Protein, Brain Tumour Resection, Inflammatory Response.

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INTRODUCTION

Brain tumor surgery as part of major intracranial surgery will trigger a significant stress and inflammatory response. Tissue trauma, nerve manipulation, and brain tissue surgery can activate the immune system and release inflammatory mediators. One of the clinical indicators commonly used to monitor systemic inflammation and post-operative complications is CRP [1]

Studies in neurosurgical patients show that after craniotomy or intracranial surgery, CRP usually increases within a few days after surgery, and a 'rise and fall' pattern in CRP can help distinguish between a physiological inflammatory response to surgical trauma and possible infection or postoperative complications [2] However, although CRP is sensitive to post-operative inflammation, its interpretation is not always straightforward because elevated CRP levels can be part of the normal response to surgery, not just the result of infection [3]

In this context, there is a clinical and research need to find strategies that can modulate the post-operative inflammatory response and improve clinical outcomes. One interesting candidate is the α₂-adrenergic receptor agonist dexmedetomidine, which has been widely used as an adjuvant sedative/analgesic in anesthesia [4]

DEXMEDETOMIDINE

Dexmedetomidine is a selective α2-adrenoceptor agonist that acts by activating pre- and post-synapses in the central nervous system. This agent causes hyperpolarization of noradrenergic neurons, inducing an inhibitory feedback loop and suppressing the release of noradrenaline, thereby achieving a sympatholytic effect [5].

This agent differs from other sedative agents in that it does not act directly on γ-aminobutyric acid (GABA). Compared to other α2-adrenoceptor agonists, dexmedetomidine has advantages in terms of pharmacokinetics due to its shorter half-life and advantages in terms of pharmacodynamics due to its higher α2:α1 adrenoceptor affinity [5,6].

Absorption of dexmedetomidine through the nasal and buccal mucosa is sufficient, making it suitable for use in uncooperative children and geriatric patients. According to European Medicines Agency, when administered orally, a significant first-pass effect

can be observed, with bioavailability of 16%.

The distribution of dexmedetomidine is facilitated by albumin and α1-glycoprotein. Studies show that dexmedetomidine is distributed widely and rapidly throughout the body. In animal studies, dexmedetomidine has been reported to rapidly cross the blood-brain barrier and the placental barrier (European Medicines Agency, 2016). The distribution half-life of this compound is approximately 6 minutes in healthy individuals. The volume of distribution under normal conditions is estimated to be 1.31–2.46 L/kg (90–194 L) [7].

After being metabolized into inactive metabolites, the compound is excreted mainly through the liver, with only 1% being eliminated through the kidneys and feces [6]. Although dexmedetomidine is almost entirely (95%) bound to albumin, hypoalbuminemia has been shown not to affect the elimination process of this compound. The average elimination half-life of dexmedetomidine is 1½ to 3 hours for intravenous administration and approximately 5 to 6 hours for intramuscular administration [8]. Because its metabolism depends on the cytochrome P (CYP) 3A4 system, interactions with other drugs are highly likely [9]. However, the studies and evidence currently available to support this claim are still very limited. One study reported that dexmedetomidine increased serum concentrations of tacrolimus up to fourfold [10].

PHARMACODYNAMICS

The sedative effect of dexmedetomidine resembles the natural sleep mechanism and deep sleep often found in patients with sleep deprivation. The sedative and hypnotic effects of dexmedetomidine are thought to be mediated by activation of pre- and post-synaptic α2-adrenergic receptors in the locus coeruleus, and dexmedetomidine also affects endogenous sleep-promoting pathways [4,11]. The exact mechanism is still unclear, but it is thought that other receptors, besides those acting on GABA, are also involved [6].

The sedative effect of dexmedetomidine depends on its concentration, with plasma concentrations of 0.2 and 0.3 ng/mL providing significant sedation but still allowing for stimulation/awakening. Deep sedation that cannot be stimulated is observed at a plasma concentration of 1.9 ng/mL [6].

The analgesic effect of α2 agonists is mediated by receptors that bind α2 in the brain and spinal cord. Pain transmission is suppressed by hyperpolarisation of interneurons and a decrease in the release of pro-nociceptive transmitters such as substance P and glutamate [12]. Studies investigating the analgesic effects of dexmedetomidine report that the exposure doses used for light and deep sedation appear to be insufficiently effective for achieving analgesic effects. When administered as a single agent in healthy patients, dexmedetomidine at a concentration of 1.23 ng/mL was unable to provide adequate analgesic effects against heat and electrical stimuli. In a crossover trial comparing the respiratory and analgesic effects of dexmedetomidine with remifentanil, it was reported that dexmedetomidine at a concentration of 2.4 ng/mL provided a weaker analgesic effect than remifentanil. It can be concluded that the analgesic effect of dexmedetomidine is still unclear and is thought to be caused by changes in perception and anxiety, although the opioid-sparing effect of dexmedetomidine has been described in several studies and anesthetic effects have been observed when using local anesthesia techniques [13].

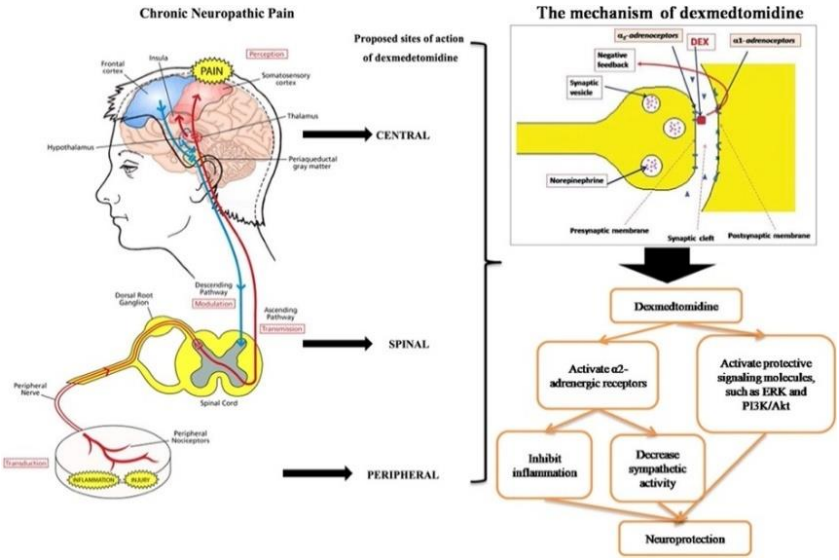

Figure 1: Illustration of the mechanism of action of dexmedetomidine for analgesic effects [14]

α2 agonists such as dexmedetomidine have gained attention in recent years due to their potential protective effects on organs. α2 agonists inhibit central sympathetic flow and reduce systemic adrenaline and noradrenaline while improving the balance between oxygen supply and demand in organs. In addition to these hemodynamic effects, dexmedetomidine also has anti-inflammatory

effects that reduce ischemic reperfusion injury and enhance anti-apoptotic pathways. α2 agonists are considered beneficial for nephroprotection and neuroprotection [15].

Dexmedetomidine is approved for intravenous use in intensive care units and for sedation procedures. When used for sedation, an initial (loading) dose of 0.5–1 mcg/kg is administered slowly over 10 minutes. At the end of this initial dosing period, most patients will be mildly sedated. Faster administration will result in a more rapid onset of sedation but is associated with hypotension and bradycardia. After the initial dose, a maintenance dose of 0.3–1 mcg/kg/hour is required. Close monitoring is necessary in elderly patients, especially those with a history of hypertension. It is recommended that this population be given the lowest possible dose for both the initial and maintenance doses mentioned above.

Dexmedetomidine administered as an off-label anesthetic adjuvant uses an initial (loading) dose of 0.5–1 mcg/kg over 10 minutes, followed by a maintenance dose of 0.3–0.5 mcg/kg/hour. When administered intranasally, a dose of 0.5–2 mcg/kg is often used. In pediatric populations, higher doses are usually administered (2 mcg), while for adults and the elderly, a dose of 1 mcg/kg is usually sufficient. The onset of clinical effects with intranasal administration of dexmedetomidine is considered rapid, occurring within approximately 15–20 minutes, with the duration of effect varying depending on the dose administered.

C-REACTIVE PROTEIN (CRP)

C-reactive protein (CRP) is a protein that was first isolated from the serum of patients suffering from pneumococcal infection. This protein differs from various capsule polysaccharides and nucleoprotein fractions of bacteria that have been successfully identified. Several decades later, an increase in protein substance was observed when exposed to inflammatory stimuli. The term CRP was adopted after the successful identification of the specific ligand for CRP in the pneumococcal 'C' polysaccharide as phosphocholine, which is a derivative of teichoic acid from the pneumococcal cell wall [16].

CRP is mainly synthesized in the right lobe of the liver in response to IL-6. Several extrahepatic organs that produce CRP include neurons, smooth muscle cells, adipose tissue, the intestine, renal cortical tubules, pulmonary epithelial cells, Kupffer cells, activated peripheral blood monocytes, alveolar macrophages, and lymphocytes. Other cytokines that also stimulate CRP production, but to a lesser extent, include IL-1ß, IL-17, TNF-α, and other stress signals released by blood vessels due to tissue damage. The cytokines IL-6 and IL-1ß control the expression of the CRP gene through the activation of the transcription factors C/EBPß and C/EBPδ, which are important for the induction of the CRP protein [17].

Within the liver cell, the pentamer is assembled in the endoplasmic reticulum while this protein binds to two carboxylesterases (gp60a and gp50b). During resting conditions and in the absence of inflammatory processes, the protein is naturally released from the reticulum. When certain cytokines increase, the strength of this bond decreases, causing the protein to be rapidly secreted in large quantities into the circulation [16].

Before receiving the stress signal induction that initiates new protein synthesis, liver cells will slowly release basal CRP that has been previously synthesized and stored in intracellular vesicles [16]. With stimulation, many new proteins will be synthesized and released 6 to 12 hours after stimulation, with an increase that can reach 1000 times the normal/basal value or more, which is usually achieved within 24 to 72 hours. The half-life of this protein is 19 hours [18].

In practice, CRP protein is often used to rule out the presence of systemic inflammatory processes in the body [19]. Currently, various studies are investigating the direct link between this protein and certain diseases. CRP can be used as an immunochemical marker for various medical conditions such as sepsis, coronary heart disease, various autoimmune diseases, malignancies, and others [16,19].

CRP protein is considered a protein in the innate immune system that provides basic protection to the body in the form of recognizable biomolecules and acts as a modulator of the host's defense responses, such as tissue barriers, vascular activation, phagocytic responses, and amplification mechanisms. The exact function of CRP depends on the form of CRP at the site of inflammation, although this is not yet clearly understood. At the site of inflammation, it is thought that changes in the conformation and structure of CRP occur, shifting from a pentameric structure to a non-native structure (e.g., a monomeric structure), indicating the presence of an inflammatory process [20].

CRP pentamer protein is most commonly found in the blood, while CRP monomer is more commonly observed in various normal tissues, particularly in the intima, media, and adventitia of blood vessels, as well as in the fibrous tissue of the skin. CRP pentamer protein is the substrate used to produce CRP monomer, so the relative levels of CRP pentamer measured in the circulation will depend on the rate of conversion of CRP pentamer to CRP monomer. This process depends on intra-subunit disulphide bonds, which determine the conversion rate and structural stability of the CRP isoform [20]. In its pentameric form, CRP is difficult to break down (proteolysis), while the monomeric form is easily broken down by various peptidases released by neutrophils. These peptides also inhibit the activation of platelets and neutrophils, reducing the potent proinflammatory activity of intact monomers [18].

Various studies have examined the relationship between CRP and various clinical outcomes in surgical and non-surgical patients. A study by Tian et al. among 5,075 patients who underwent heart valve surgery, those with CRP levels >5 mg/L reported a higher risk of heart failure and death within 30 days after surgery [21]. Another study by Shetty et al. on 51 patients who underwent bone surgery, levels >24 µg/mL reported a significant risk of post-operative bone infection [22]. Approximately 60% of all patients with post-operative bone infection had CRP levels of 96 µg/mL. In non-surgical cases, a study by Su et al. on populations with mild head

injuries, an increase in CRP from baseline increases the risk of patients developing post-concussion syndrome (PCS), psychological disorders, and persistent cognitive impairment [23].

DEXMEDETOMIDINE AND NEUROSURGERY

The use of dexmedetomidine for neurosurgery is common because this drug has analgesic and sedative effects while allowing patients to remain responsive for organ function monitoring. Several uses of dexmedetomidine in neurosurgery are summarized in Table 1 [24].

Table 1: Use of dexmedetomidine as a sedative, premedication, or anaesthetic adjuvant [8,25]

Surgical Procedures	Description
Dexmedetomidine for sedation	
Electrode implantation in deep-brain stimulation (DBS)	Dexmedetomidine has a moderate effect on brain electrophysiological function compared to other GABAergic sedation alternatives, allowing for more accurate DBS placement.
Awake craniotomy	Dexmedetomidine provides sedation similar to natural sleep, making patients more cooperative. Its disadvantage lies in its minimal amnesic effect compared to other alternatives such as propofol.
Awake fibreoptic intubation	Dexmedetomidine may be beneficial for this surgical procedure, but further research is needed. Intranasal dexmedetomidine may be beneficial for sedation in anxious and uncooperative patients without intravenous access, such as children or adults with cognitive impairment. Caution should be exercised when administering to elderly patients, as it may cause hypotension.
Dexmedetomidine as an anaesthetic adjuvant	
Intracranial or neurovascular tumour surgery	Although theoretically beneficial, further research is still needed.
Intraoperative monitoring during spinal surgery	Dexmedetomidine assists in propofol-sparing techniques because it works synergistically to enhance the effects of propofol while having minimal effects on motor and somatosensory functions.
Prevention of delirium	The use of dexmedetomidine for sedation in intensive care units is associated with a lower risk of delirium.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or internal globus pallidus (GPi) is a common treatment for Parkinson's disease and various other dystonias [26]. The DBS procedure is also applied in the management of Tourette's syndrome and is believed to be beneficial in the future for obsessive compulsive disorder (OCD), obesity, and depression [27]. The implantation of the necessary hardware involves fixing the navigation frame of the device into the skull using sharp pins, followed by evaluation using a local computed tomography (CT) scan of the area being worked on, then installing electrodes, a subcutaneous impulse generator, and cables connecting the electrodes and impulse generator. To facilitate accurate and optimal DBS electrode implantation, the following are required: functional examinations before, during, and after implantation, intraoperative neurophysiological testing, local action potential recording, mapping processes with microelectrode readings (MERs), and stimulation testing [24]. Due to this requirement, the use of general anesthesia and sedation would hinder DBS implantation and interfere with intraoperative evaluation and recording. Some healthcare institutions have attempted to use local anesthesia, but unsedated patients are more likely to experience discomfort, anxiety, and stress during surgery [28]. Excessive stress during surgery can trigger motor tics, dystonia, and tremors that will hinder surgical procedures and imaging. Therefore, anxiolytic and sedative agents are still required for DBS procedures [27].

Dexmedetomidine has advantages over propofol and other benzodiazepines for DBS procedures. Several studies argue that with optimal titration, propofol and benzodiazepines can also provide mild anxiolysis and mild sedation suitable for DBS. However, propofol and benzodiazepines are GABAergic agents, so they affect clinical manifestations (such as tremors) in patients even when administered in small doses. In addition, both agents suppress neuronal conduction velocity and interfere with MER, increasing the stimulation threshold, which ultimately affects marksotimulation [29]. Dexmedetomidine has minimal effects on the electrophysiological functions of the brain, such as conduction velocity and amplitude, although this also depends on the method of administration, dosage, and recording location. The use of the appropriate dosage is considered safe and effective without interfering with clinical assessment and MERs during the DBS implantation process [30].

Awake craniotomy is a frequently performed procedure divided into three main phases. Although this procedure is usually performed under local anesthesia, sedation or general anesthesia is usually still administered because the patient is awake during phase one (the

patient's head is secured with a Mayfield clamp for surgical assessment) to phase three (closure of the head). Patients often experience anxiety and agitation, so sedation is necessary, especially during the second phase. When sedation is administered, an anesthesiologist is required to balance comfort and safety while keeping the patient lucid so that they can cooperate during intraoperative neurological examination. For optimal comfort, local anesthesia or intravenous medication may be administered. Inadequate sedation results in stress, hypertension, myalgia, and fatigue, which will make it difficult for the patient to be cooperative during the procedure [24].

Awake craniotomy is the gold standard technique for removing brain tumors in specific areas. Maximum tumor resection while preserving brain function as much as possible is important in these cases. Some areas of the brain have essential functions in life, such as motor, language and cognitive functions [31]. The use of brain-evoked potential techniques, neurophysiological testing, and real-time imaging techniques such as magnetic resonance imaging (MRI) or CT scans will increase the likelihood of maintaining physiological function after tumor removal surgery [32].

Dexmedetomidine once again demonstrated its superiority in this craniotomy procedure due to its anxiolytic, sedative, and analgesic (mild) effects, coupled with minimal to no respiratory depression. A limitation of dexmedetomidine is that at the recommended dose, patients may experience mild amnesia, unlike propofol, which can be administered in smaller doses and results in amnesia throughout the procedure. Since the analgesic effect of dexmedetomidine is mild, remifentanil is typically administered concurrently for better pain control [33].

NEUROSURGERY AND C-REACTIVE PROTEIN (CRP) LEVELS

Postoperative surgical site infection (SSI) following neurosurgery is a significant complication with an incidence rate of 0.8–7%. By definition, SSI occurs 30 days after surgery and can be classified as scalp infection, bone flap osteomyelitis, subdural empyema, brain abscess, and/or meningitis. Neurosurgery patients involve various devices such as ventricular drains, intracranial sutures and bolts, bladders, and intravenous catheters. All these factors, combined with the type and duration of prolonged surgery, increase the risk of infection. The onset of SSI can be difficult to distinguish from other infections that show similar symptoms. Postoperative changes that commonly occur are often caused by openings/tears in the dura and the breakdown of blood products, which cause symptoms such as fever, confusion, and meningismus. Confirmation of a diagnosis of meningitis can be established by culture isolation or Gram staining, although in 70% of suspected cases, cerebrospinal fluid (CSF) culture often shows negative results [2]. Currently, the assessment of post-operative patients' readiness to be discharged is based on clinical observations supported by serum inflammatory marker tests. Many biological markers have been proposed for the detection of ILO, one of which is CRP protein. CRP protein is considered sensitive for measuring systemic inflammatory responses. Unfortunately, despite its sensitivity, the use of CRP for detecting post-operative infection remains limited because its levels are often reported to increase post-operatively [2].

Study by Sharouf et al. evaluating CRP kinetics reported that both patients with ILO and without ILO will experience an increase in CRP, peaking on the second day after surgery [2]. However, in patients with ILO, a significant increase of up to twice the normal value will be observed compared to those without ILO (median CRP 115 mg/L vs. 57 mg/L; $p<0.001$). In the group without ILO, CRP will gradually decrease from the second day after surgery to normal values on the fourth day after surgery. In the group with ILO, CRP will rise again on the 5th day post-surgery ($p<0.001$) (Figure 2). An increase in CRP on the 5th day or failure of CRP to decrease to normal levels has a sensitivity of 71%, specificity of 90%, and negative predictive value of 96% for detecting early post-surgical infection. A comparison of CRP levels in neurosurgical operations versus other surgeries is summarized in Table 2 [2].

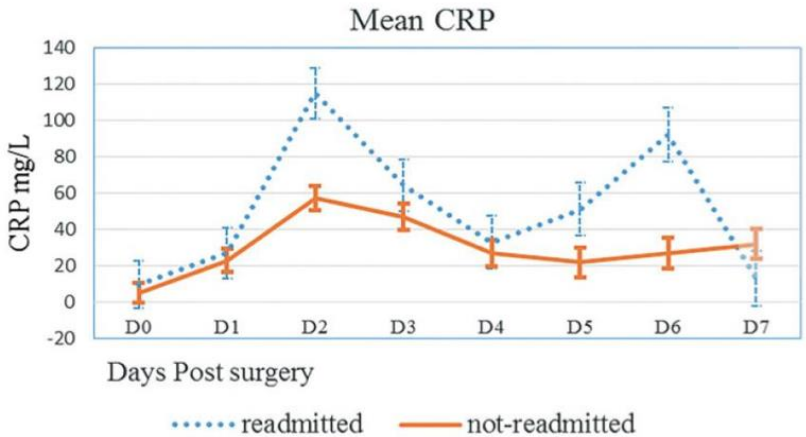

Figure 2: CRP value changes from day 0 (DO) to day 7 (D7) post-surgery in patients who returned with and without surgical site infections. All patients were post-neurosurgery patients [2]

Table 2: Summary of CRP levels in various types of surgery, including neurosurgery, spinal surgery, pelvic surgery, and abdominal surgery (Sharouf et al., 2020)

Postoperative CRP	D0	D2	D3	D4
Intracranial (without infection) [2]	10	27	57	22
Intracranial (with infection) [2]	5	23	115	51
Intracranial (microsurgery) [34]	5	32	22	10
Intracranial (without infection) [1]	5	204	160	130
Intracranial (with infection) [1]	10	194	175	188
Intracranial (tumor) [35]	4	167	-	-
Neurosurgery (without infection) [36]	5	75	60	25
Neurosurgery (with infection) [36]	10	150	150	175
Single Posterolateral interbody fusion (PLIF) [37]	4	127	-	60
Total hip replacement [38]	10	150	110	50
Abdominal surgery (without complications) [39]	60	196	160	105
Abdominal surgery (with complications) [39]	60	282	255	180

Higher CRP levels are associated with poorer neurological outcomes. A study by Bahorik et al. reported that high and moderate increases in CRP were significantly associated with slower thinking speed and poorer executive function [40]. The REGARDS (REasons for Geographic and Racial Differences in Stroke) clinical study also reported that high CRP levels were associated with poorer memory and verbal function [41]. Unfortunately, the data currently available regarding neurological function outcomes are mostly reported in non-surgical populations, so research linking CRP levels to neurological function in post-surgical populations, particularly neurosurgery, is still needed.

DEXMEDETOMIDINE AND C-REACTIVE PROTEIN (CRP) LEVELS

Research with test animals shows that dexmedetomidine suppresses serum and tissue inflammatory mediators. Various studies in humans have also proven this, where dexmedetomidine has been reported to reduce levels of CRP, TNF-α, IL-6, and IL-1ß proteins after heart bypass surgery and spinal surgery [42,43]. In a non-surgical setting, the use of dexmedetomidine in patients with sepsis receiving mechanical ventilation showed CRP levels (range, 5.6–20.3 vs. 8.3–21.1 mg/dL; p=0.03) and procalcitonin (range, 1.2–37.4 vs. 1.7–52.9 ng/mL; p=0.04) levels compared to the group not receiving dexmedetomidine [44].

INTEGRATION OF RESEARCH FINDINGS ON CRP REGULATION BY DEXMEDETOMIDINE

Dexmedetomidine is an α_2-adrenergic agonist known to have potent sedative, sympatholytic, and anti-inflammatory effects. Several studies have shown that this drug is able to suppress the release of norepinephrine and reduce sympathetic system activation, which ultimately inhibits the production of inflammatory mediators such as IL-6, TNF-α, and IL-1β [42–45]. Since CRP is primarily influenced by IL-6, the reduction of these inflammatory mediators can biologically contribute to a decrease in postoperative CRP levels. Therefore, the biological basis for the potential of dexmedetomidine in suppressing the inflammatory response has been well established in various interdisciplinary surgical studies.

However, the relevance of these findings in the context of brain tumor resection needs to be analyzed more carefully [46]. The literature shows that post-intracranial surgery CRP exhibits a significant physiological increase due to tissue trauma. CRP usually peaks on the second day and decreases on the fourth day if there are no complications of infection [2], while a pattern of continued increase often indicates infection or prolonged inflammation [36]. This pattern is greatly influenced by the duration of surgery, the extent of brain tissue manipulation, transfusions, and other perioperative factors. Given these conditions, the anti-inflammatory effects of dexmedetomidine that are clearly evident in other surgeries may be less pronounced or more difficult to detect in intracranial surgery.

In neuroanesthesia, the use of dexmedetomidine is more frequently reported to be associated with hemodynamic stability, sedation quality resembling physiological sleep, and minimal respiratory depression, which are highly relevant advantages in procedures such as awake craniotomy [24,32]. Yet, no studies have directly evaluated the effect of dexmedetomidine on CRP levels in patients undergoing brain tumor surgery. Most evidence showing a decrease in CRP comes from non-intracranial surgery, so generalizing these findings to the neurosurgical population has methodological limitations.

Additionally, perioperative factors such as high-dose steroid administration, intraoperative opioid use, different anesthesia techniques, and significant variations in tissue trauma intensity also influence postoperative CRP levels. These variables may act as confounders, making it difficult to assess whether changes in CRP are truly influenced by dexmedetomidine or by other perioperative interventions.

CONCLUSION

Based on a review of the literature, dexmedetomidine shows significant potential as an agent capable of modulating the postoperative inflammatory response. The sympatholytic mechanism and anti-inflammatory effects of this drug support the finding that dexmedetomidine can reduce inflammatory mediators, including CRP. In the context of brain tumor resection surgery, where elevated CRP is a common phenomenon due to surgical trauma, the use of dexmedetomidine has the potential to help suppress excessive inflammatory responses and may contribute to better postoperative outcomes. However, direct evidence in brain tumor populations remains limited, necessitating specific clinical studies to confirm its benefits in reducing CRP, the risk of surgical site infection, and postoperative neurological function.

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