Review Article

Neuroprotective Strategies in the Perioperative Period: A Systematic Review

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Abstract

Surgery and anesthetics may cause brain damage, and the resulting neurological defect can impair the patient's cognitive function. This disorder is one of the most common complications after surgery and causes disorders in several cognitive areas of the patient. The mechanism of this disorder is not fully understood, but neuronal inflammation is one of the main causes of this disorder. The purpose of this systematic review was to evaluate neuroprotective drug strategies for the treatment or prevention of surgical disorders associated with anesthesia. We searched the keywords "neuroprotective", "neuroprotection", "postoperative" and "perioperative" in the databases of the web of science, Scopus, PubMed, ScienceDirect, and Google Scholar with a 5-year time limit. At first, 492 articles were obtained, and finally, after a detailed survey based on exclusion and inclusion criteria, 31 studies were selected to extract data. Findings from studies show that medication and treatment strategies used in a group of mice and rats under surgery with treatment can improve Neuronal inflammation and brain damage compared to mice and rats with surgery only and reduce the side effects of surgery and anesthetics.

Keywords: Perioperative Period, brain injury, Neuroprotection

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Introduction

Postoperative cognitive dysfunction is a clinical complication in the central nervous system that is known as one of the most significant postoperative complications and causes disorders in several cognitive areas such as memory, concentration, learning, and speaking disorders Becomes (1). This disorder can occur in patients with mild to severe, these disorders when are severe and long-lasting may also increase the risk of death (2, 3).

The mechanism of complete cognitive dysfunction has not been determined, but the results of previous studies showed that neuritis caused by general anesthesia and surgery was one of the main causes of this disorder (4-7). The results of various clinical studies showed that increased levels of serum pro-inflammatory cytokines might be associated with impaired postoperative cognitive function, (8, 9) regulation of inflammatory cytokines in the hippocampus after surgery, and macrophage infiltration. It occurs in the brain and activates the glia (10, 11) and by inhibiting macrophages and neuritis, cognitive dysfunction is reduced (10). Results of in vivo studies showed that there is a link between

cognitive dysfunction and neuroinflammation (4, 12-13). Therefore, neuroinflammation after surgery can cause synaptic dysfunction and apoptosis in the hippocampus. However, the results of the studies show only inflammation. Neurological does not lead to cognitive dysfunction (14-16).

For example, the results of a study by Zhang et al. On mice showed that the expression of inflammatory mRNA molecules such as TNF-α, IL-1β, and IL-6 increased after surgery in mice receiving anthocyanin. They inhibit their effects and the expression of these molecules was significantly reduced. IBA1 was also increased as a microglial marker in the hippocampus after surgery, but mice receiving anthocyanin were able to inhibit its effect and reduce its expression. Hippocampal cell apoptosis was also reduced in drug-treated mice, unlike other mice. (17).

In a study by Ye et al., Inhibition of IBA1 expression and inflammatory mRNA molecules and reduced apoptosis of hippocampal neurons were observed in operated mice receiving Honokiol (18). However, in Zhang et al.'s study, the levels of TNF-α, IL-1β, and IL-6 were not significantly different between operated mice and operated mice receiving lipopolysaccharide (19).

Results of previous studies showed that neuritis could play an important role in the development of cognitive dysfunction, therefore, therapeutic and anti-inflammatory strategies can reduce cognitive dysfunction by inhibiting inflammation. The purpose of this systematic review study was to review neuroprotective strategies for the treatment or prevention of surgical disorders.

This systematic review study was performed based on the Prism checklist. To prevent bias in the study, the method of searching databases, selecting studies based on input and output criteria, evaluating the quality of studies based on the ARRIVE checklist, and extracting information from studies were performed by two researchers independently. The opinion of the third researcher applies when there was no agreement between the two authors.

Study Method

Search Strategy: Keywords "neuroprotective", "neuroprotection", "postoperative" and "perioperative" were searched in the web databases of science, Scopus, PubMed, ScienceDirect, and Google Scholar. Only articles published in English were reviewed. First, the titles and abstracts of the articles obtained from the search were reviewed, and then the articles that were selected were reviewed based on the input and output criteria so that finally the articles that were eligible to extract the required information. A 5-year time limit (2016-2020) was set for the search. This systematic review study was performed based on the Prism checklist.

Study selection: Only articles in English were reviewed and articles in other languages were excluded. We reviewed human studies, duplicates, studies of animals tested for disease (such as diabetes), articles that examined only the effects of anesthesia on animals without surgery, and a variety of case series, case reports, conference abstracts, editorials, letters to the editor and commentaries were identified and removed from the study.

Quality assessment: the methodological quality assessment of the selected articles based on the ARRIVE guideline (has been prepared to increase the quality of methods and results of experimental and laboratory studies on animals) was independently reviewed by two reviewers (20). Each of the different sections of the study such as title, abstract, introduction, methodology, findings, and discussion were matched with 20 items of ARRIVE instructions.

Data extraction and Processing: we extracted the species tested, their number, sex, and age, type of surgery, anesthetic used, a drug used to evaluate its neuroprotective mechanism, doses of the drug used, and a summary of results from the studies. One reviewer extracted the required information from the selected studies and entered it in the table. This information was carefully reviewed by the second reviewer and in case of disagreement between the first and second reviewer, the third reviewer was used. If the full text of the article or the required data was not available, we sent an email to the author of the article requesting the full text of the article or the required data to be provided to us for information retrieval.

Results

After searching for keywords in Scopus, Web of Science, ScienceDirect, PubMed, and Google Scholar databases, we obtained 492 articles for the period 2016 to 2020. After deleting 114 duplicate articles, 378 studies remained to review the title and abstract. After carefully reviewing the titles and abstracts of 378 articles, 269 studies due to being human, repetitive, non-English language, non-surgical, sick animals, case reports, conference abstracts, editorials, letters to the editor, commentaries the study was deleted. 109 articles were selected for more detailed review, the full text of 109 articles was carefully reviewed, and finally, 31 studies were included in the study due to the required information, and their information was extracted. The article search process and the number of selected and deleted articles based on the input and output criteria are summarized in the flow diagram (Figure 1).

A summary of the characteristics of 31 studies, including items of type and number of animals tested, type of surgery, anesthesia, the drugs used to evaluate the effects on neuroprotection, doses used, and also a summary of the results are given in Table1.

Animals: in 14 studies mice (17-19, 21-31) and 17 studies Rat (32-48) were used for studies. In most studies (83.8%) only males had been used. The reason for using males in most studies was to eliminate the effect of female sex hormones on cognitive dysfunction and also to eliminate weight differences. Males weigh were less (30). In 15 studies of Sprague Dawley rats, 11 studies of C57BL/6 male mice, and each of CD-1 mice, F344XBN F1 rats, Wistar rats, and Kunming mice were used once in 31 studies selected for testing.

Anesthesia drugs: data extracted from 31 studies showed that in 12 studies, from the anesthetic Isoflurane (19, 17, 21-30), 6 studies from the anesthetic Sevoflurane (18, 31-35), one study from pentobarbital (36), and 4 studies from pentobarbital sodium (37-40), chloral hydrate alone (41-44) was used in 4 studies and chloral hydrate with lidocaine was used in one study (45). In three other studies, anesthetics halothane (46), fentanyl in combination with droperidol (47), and bupivacaine (48) were used for surgery in mice or rats.

Anthocyanin: the drug was used in one study, despite a significant increase in phosphorylation of MLK3, p38 MAPK, and JNK in operated mice compared with the control group (P<0.01), both doses of 100 and 50 mg/kg phosphorylation level in mice undergoing surgery and receiving medication, decreased significantly (P<0.01).

Significantly increased expression of the protein (IBA-1) molecule 1 ionized calcium-binding adapter induced by surgery (P<0.01), decreased significantly with each dose (P <0.01). Neuronal apoptosis and expression level of pro-inflammatory cytokine molecules were also significantly reduced after surgery (P<0.01) after receiving treatment (P<0.01) (17).

Fingolimod (FTY720): using this drug in mice undergoing surgery significantly reduced the activity of microglia in the CA1 region of the hippocampus (p <0.05) (21). An abnormal increase in microglia activity is directly related to neuroinflammation and increases neuroinflammation, thus increasing the likelihood of cognitive dysfunction (4). Syn, psd95, and ampar proteins, which are glur2 subunits, are involved in postoperative cognition. Glur2 and psd95 protein levels should be significantly reduced after surgery (p <0.05) with Fingolimod (fty720). Increased significantly (p <0.05). However, the level of Syn protein did not change much after surgery (p> 0.05) and also the administration of the drug did not affect its level (p> 0.05) (21).

RO 61-8048: macrophages activated by immune cytokines that result from postoperative brain damage stimulate the production of kynurenine in the brain, which binds kynurenine to its target receptors in microglia and astrocytes to produce kynurenic acid (KYNA) and quinolinic acid (QUIN) becomes. QUIN can cause nerve poisoning. QUIN increased significantly after surgery (p <0.01) while receiving RO 61-8048 in these rats could significantly reduce its expression (p <0.01). KYNA expression also increased significantly after surgery compared to the control group (p <0.01) and also received treatment significantly increased its expression compared to rats who underwent surgery and did not receive treatment (p <0.01). Pro-apoptotic Bax markers were significantly decreased (p <0.01) using RO 61-8048 treatment and also anti-apoptotic BCLxl and BCL2 markers were significantly increased (p <0.01) (32).

Table 1. Characteristics of studies with neuroprotective strategies

ID	Animal (Number)	Surgery	Anesthesia drug	Drug/inhibitor	Doses	Outcome	Ref
1	Adult male CD-1 mice (24)	exploratory laparotomy	Isoflurane	Anthocyanin	50 mg/kg 100 mg/kg	• phosphorylation of MLK3, p38 MAPK, and JNK in the hippocampus ↓ • IBA1 protein expression level ↓ • apoptotic cells ↓ • mRNA expression levels of inflammatory molecules (TNF-α, IL-1β, and IL-6) ↓	(17)
2	2-month-old male C57BL/6J mice (48)	Hepatic lobectomy	Sevoflurane	Fingolimod (FTY720)	1 mg/kg	• activated microglia in CA1 at 6 hours and 3 days after surgery ↓ • The expression of PSD95 and GluR2 protein ↑ • The expression of SYN protein ▬	(21)
3	adult male Sprague-Dawley rats (127)	craniotomy	Isoflurane	RO 61-8048	40 mg/kg	• expression of QUIN ↓, KYNA expression ↑, pro-apoptotic BAX ↓ , and anti-apoptotic markers BCLxl and BCL2 ↑	(32)
4	15~16-month-old male Sprague Dawley rats (45)	cardiopulmonary bypass	pentobarbital	Dexmedetomidine	50 ug/kg	• the concentration of IL-β, IL-6, and TNF-α ↓ • IBA-1 positive cells in hippocampus and prefrontal cortex ↓ • The content of Aβ and Tau in the hippocampus, prefrontal cortex, and plasma ↓ • apoptotic cells in the hippocampus and prefrontal cortex ↓ • expression of Bax, Bcl-2, and Caspase-3 in the hippocampus, prefrontal cortex ↓	(33)
5	20-month-old Male Sprague-Dawley rats (80)	splenectomy	pentobarbital sodium	vitamin-rich carbohydrate	12 ml	• expression levels of GRP78 and eIF2a in the hippocampus ↓ • Beclin-1, Bax↓ , and Bcl-2 levels ↑	(34)

6	18-month-old male Sprague-Dawley rats (75)	splenectomy	pentobarbital sodium	Dexmedetomidine	12 μg / kg	• expressions of TNF-α and IL-1β ↓ • ameliorated in neuronal morphology and arrangement • neuronal apoptosis index in the hippocampal CA1 region ↓ • the protein expressions of $GABA_BR1$ and $GABA_BR2$ ↓, PKA, BDNF, and p-CREB ↑, CREB ▬	(35)
7	18-20 months old male Sprague-Dawley rats (120)	hepatectomy	isoflurane	Exendin-4	5 μg/kg	• the protein level of NF-κB p65 and IL-1β at 7 days after surgery ↓ • protein expression of GLP-1 and GLP-1R ↑, Iba-1 ↓, and p-GSK-3β ↑ in the hippocampus at 7 days after surgery • synaptophysin expression in the hippocampus at 7 days after surgery ↑ • levels of tau hyperphosphorylation at Ser396 and Ser199/202 ↓	(36)
8	Male 24–25 months old C57BL/6J mice (75)	abdominal surgery	isoflurane	Methane-rich saline	16 ml/kg	• TNF-α and IL-6 cytokine expression level ↓ TNF-α and IL-6 transcription levels ↓ • phosphorylation of ERK, JNK, P38, and P65↓ • The cell body-to-cell size ratio ↓ • decreasing the activated level of IBA1-positive cells	(22)
9	4-month-old adult female C57BL/6J mice (24)	abdominal exploratory surgery	sevoflurane	Honokiol	10 mg/kg	• expression levels of LC3-II and Beclin-1 ↑ • PINK1 and Parkin protein expression ↑ • The levels of MDA and Mitochondrial ROS ↓ • expression of NLRP3, ASC, Caspase-1, IL-1β IL-18, and Iba-1 ↓ • neuronal apoptosis in the hippocampal CA1 and DG regions ↓	(23)
10	4-month-old adult female C57BL/6J mice (84)	exploratory laparotomy	sevoflurane	Honokiol	10 mg/kg	• neuronal apoptosis in the hippocampal CA1 and CA3 regions ↓ • expression levels of TNF-α, IL-1β, MCP-1, and IBA-1 in the hippocampus region↓ • level of MDA, Mitochondrial ROS, and cytochrome C ↓ • expression levels of SIRT3 ↑, Ac - SOD2 ↓ and SOD2 ▬	(18)
11	4–5-month-old male wild-type C57BL/6J mice (24)	abdominal surgery	isoflurane	Ginsenoside Rg1	10 mg/kg	• levels of ROS ↓ • basal mitochondrial respiration levels ↑ • ATP production ↑ • maximal mitochondrial respiratory capacity↑ • uncoupling capacity↑ • levels of mitochondrial membrane potential↑ • sirt3 expression and deacetylation activity↑	(24)

12	18-month-old male Sprague–Dawley rats (100)	intramedullary fixation of a tibial fracture	chloral hydrate	purmorphamine	15 mg/kg	• the protein expression of Shh, LC3-II, LC3-II / LC3-I ↑ , and P62 ↓	(37)
13	3-month-old C57BL6/N mice (-)	laparotomy	sevoflurane	Siegesbeckia Orientalis	0.75 g/kg (low dose) 1.5 g/kg (high dose)	• regulation of IL-6 and IL-1β in high dose ↓ and low dose ▬ • regulation of IL-8 and TNF- α in all doses ▬ • phosphorylation of JNK and p65 in high dose↓ and ▬ low dose • Tau phosphorylation in the hippocampus at all doses↓	(25)
14	aged male F344XBN F1 rats (-)	laparotomy	halothane	Mycobacterium vaccae immunization	0.1 mg	• Hippocampal IL-1β gene and protein expression in aged rats ↓ • upregulated IL-4, Arginase1↑ , and NFKBIA↓ mRNA expression in aged rats • CD3↓ , CD4 ▬ , and FOXP3↑ mRNA expression in aged rats	(38)
15	19-22 month old wistar male rats (94)	abdominal surgery	isoflurane	emulsified form of resveratrol	80 mg/kg 60 mg/kg 40 mg/kg 20 mg/kg 2 mg/kg	• levels of hippocampal IL-1 β and TNF- α↓ at 80, 60 and 40 mg/kg doses • levels of hippocampal IL-1 β and TNF- α ▬ at 20 and 2 mg/kg doses	(39)
16	Male Sprague-Dawley rats (25)	exploratory laparotomy	isoflurane	Dexmedetomidine	3 μg/kg 12 μg/kg	• The number of DCX positive cells in the DG of the hippocampus ↑ at all doses • Levels of IL-1β and IL-6 and TNF-α gene expressions ↓ at all doses • BDNF gene and protein expression ↑ at all doses • p-CREB/CREB and PKA production ↑ at all doses • p-MAPK/MAPK ratio ↓ at all doses	(40)
17	18-month-old male Sprague Dawley rats (60)	Partial hepatectomy	Fentanyl + droperidol	Nicotine	0.5 mg/kg	• the protein expression levels of the pro-inflammatory cytokines IL-1β, TNF-α, HMGB-1, and NF-κB p65 in the hippocampus at 1 and 3 days after surgery ↓ • levels of IL-1β↓ , TNF-α ▬ , and HMGB-1↓ at 1 day and 3 days after surgery • BDNF and p-TrkB expression in the hippocampus ↑ at 1 day and ▬ 3 days after surgery • expression of cleaved caspase-3 in the hippocampus ↓ at 1 and 3 days after surgery • neuron Apoptosis in the CA1 Region ↓ at 1 and 3 days after surgery	(41)

18	18-month-old male Sprague-Dawley rats (96)	Exploratory laparotomy	sevoflurane	Nimodipine	1 mg/kg	• hippocampal neuroapoptosis and $[Ca^{2+}]_i$ rate ↓ at 1 and 7 days after surgery • The expression of CaN and caspase-3 ↓ at 1 and 7 days after surgery	(42)
19	12-14-month-old C57BL/6 male mice (172)	Exploratory laparotomy	isoflurane	lipopolysaccharide	0.2 mg/kg	• Levels of TNF-α ↓ , IL-1β ↓, IL-6 ↓ , and IL-10 ▬ at 24 hours after surgery (LPS administration at 72 h and 24 h before surgery) • Levels of TNF-α ▬ , IL-1β ▬, IL-6 ▬ , and IL-10 ▬ at 24 hours after surgery (LPS administration at 6 h and 0 h before surgery) • the number of hippocampal IBA1 positive cells in the hippocampus ↓ (LPS administration at 72 h and 24 h before surgery)	(19)
20	8-week old male C57BL/6J mice (48)	Carotid endarterectomy	isoflurane	Brilliant Blue G	50 mg/kg	• The expression of P2X7 receptors, precursor caspase 1 and P20 ↓ at 6 hours and 7 days after surgery • Levels of Iba-1 in the DG and CA1 region ↓ at 6 hours and 7 days after surgery	(26)
21	6-month-old Adult male Sprague–Dawley rats (40)	osteotomy	isoflurane	H_2	2%	• Levels of TNF-α ▬, IL-1β↓, IL-6↓, and HMGB1↓in serum and hippocampal • Caspase-3 activity ↓	(43)
22	16-month-old male Kunming mice (96)	partial hepatectomy	chloral hydrate	hydrogen-rich saline	10 ml/kg	• Levels of TNF-α ↓ and IL-1β ↓ in hippocampal at 8, 10, and 14 days after surgery • the activity of NF-κB ↓ in hippocampal at 8, 10, and 14 days after surgery • The optical density of TNF-α ↓ and IL-1β ↓ in hippocampal at 8, 10, and 14 days after surgery	(27)
23	14-month old C57BL/6 female mice (96)	abdominal surgery	bupivacaine	edaravone	3 mg/kg	• neuronal death in the hippocampal region ↓ • the expression of GRP78 ↓ and CHOP↓ • neuron apoptosis in the hippocampal region ↓	(28)
24	8-9 weeks adult male Sprague-Dawley rats (96)	cardiopulmonary bypass	chloral hydrate	α7nAchR agonist PHA568487	0.8 mg/kg	• neuronal apoptosis in the Hippocampal tissues ↓ • the expression of Caspase-3 ↓ at 3 and 6 hours after surgery • serum levels of S100β ↓, TNF-α ↓ and IL-6 ↓ at the end of the surgery, 3 and 6 hours after surgery • the expression of p-Akt ↑ and p-GSK3β ↑	(44)

						• the expression levels of total Akt ▬ and total GSK3β ▬	
25	18-month-old male Sprague-Dawley rats (120)	splenectomy	isoflurane	Nimodipine 7.5% Hypertonic saline	1 mg/kg 4 ml/kg	• Apoptosis and $[Ca^{2+}]_i$ rate of hippocampus neurons ↓ at 1 and 7 days after surgery • Expression of Bax↓ and Bcl-2 mRNA↑ at 1 and 7 days after surgery • Bax/Bcl-2 ratio ↓ at 1 and 7 days after surgery • the nuclear condensation, chromatin margination, mitochondrial vacuolization, and endoplasmic reticulum swelling were attenuated at 1 and 7 days after surgery • Apoptosis and $[Ca^{2+}]_i$ rate of hippocampus neurons ↓ at 1 and 7 days after surgery • Expression of Bax↓mRNA at 1 day after surgery • Bcl-2 mRNA↑ at 1 and 7 days after surgery • Bax/Bcl-2 ratio ↓ at 1 and 7 days after surgery • the nuclear condensation, chromatin margination, mitochondrial vacuolization, and endoplasmic reticulum swelling were attenuated at 1 and 7 days after surgery	(45)
26	Adult (9-month-old) and aged (18 months old) C57BL/6 mice	Splenectomy	isoflurane	glycyrrhizin	60 mg/kg	• levels of HMGB1 and TLR4 protein ↓ in the hippocampus of the aged mice • expression of synapsin I ▬ and PSD95 ↑ in the hippocampus of the aged mice • levels of the nuclear ↓ and cytosolic protein NF-κB ↑ in the hippocampus of the aged mice • Levels of IL-1β↓, TNF-α↓, and IL-6↓ in the hippocampus of the aged mice • levels of p-Tau at the site of AT-8 and Ser396 in the aged mice ↓ • levels of BACE1↓ in the aged mice • levels in either soluble Aβ40 and Aβ42 fraction or formic acid-extracted fraction ↓	(29)
27	Postnatal day 7 male and female Sprague-Dawley rat (-)	The surgery was a right carotid artery exposure	sevoflurane	Pyrrolidine dithiocarbamate	-	• concentrations GDNF↑ and BDNF ▬ in the hippocampus • cells positive for both BrdU and NeuN ↑ • expression of Iba-1 ↓	(46)

28	adult male Sprague Dawley rats (96)	cardiopulmonary bypass	pentobarbital sodium	Dexmedetomidine	5 μg/kg (high dose) 2.5 μg/kg (low dose)	• (high dose): levels of S100β↓and NSE↓ in plasma at 1 and 2 hours after surgery • (low dose): levels of S100β↓ and NSE↓ at 2 hours after surgery • The apoptosis rate of hippocampal CA1 and cortex region neurons ↓ at all doses • Levels of IL-6↓ and IL-10 ═ in the cortex region at all doses • (all doses): levels of IL-6↓at 2 hours after surgery and IL-10 ═ at 1 and 2 hours after surgery in plasma • expression of the cleaved caspase-3 protein↓ in the hippocampus at all doses • expression of pJAK2↓ and pSTAT3 ↓proteins in the hippocampus at all doses	(47)
29	Aged mice (120)	appendectomy	pentobarbital sodium	minocycline	45 mg/kg	• Levels of IL-1 β, TNF- α, IFN-γ, and Iba-1 in the hippocampus ↓ • Levels of IL-4 and IL-10 ↑	(30)
30	18-month-old male Sprague-Dawley rats (36)	abdominal laparoscopy	chloral hydrate	Deferoxamine	100 mg/kg	• Iron concentration in hippocampal ↓ • The expression of ferritin↓, Caspase-3↓, Bax ↓at 1,3 and 7 days after surgery and Bcl-2↑ at 1 day after surgery • numbers of positive-cell in DG, CA1, and CA3 region ↓ • The average cell body size↓ and cell body to cell size ratio ↓ • integrated optical density ↓ • levels of reactive oxygen species↓ at 1, 3, and 7 days after surgery, Malondialdehyde↓ at 1 and 3 days after surgery, and superoxide dismutase↑ at 1 day after surgery • expression of Fpn-1 ↓ at 1, 3, and 7 days after surgery, hepcidin ↓ at 1 and 3 days after surgery, DMT1 ↓ at 1 and 3 days after surgery, and TfR ↑ at 1, 3, and 7 days after surgery	(48)
31	12~14-month-old C57BL/6J male mice (-)	Abdominal exploratory	chloral hydrate+ lidocaine	Deferoxamine	100 mg/kg	• Iron concentration in hippocampal ↓ • The expression of CD68 ↓ and BDNF↑ • Levels of Fpn-1 ↑, hepcidin ↓, DMT1 ↓, TNF-α ↓, IL-1β ↓, MDA↓ , and ROS↓ in the hippocampus	(31)

Dexmedetomidine: it has been used in 4 studies and its use in mice and rats undergoing surgery significantly reduced the expression of pro-inflammatory cytokines (33,35,40,47). In the study of Chen et al., No significant change was observed in IL-10 levels in the plasma and cortex region in treated rats receiving treatment (47).

Neuronal apoptosis has also been studied in 3 studies, which have been significantly reduced (47,35,33). Marker levels of IBA-1, Aβ, and Tau content and expression of BAX, BCL-2, and caspase-3 were significantly decreased in the hippocampus and prefrontal cortex (33). In the study by Zhu et al., The results showed that the expression of GABABR1 and GABABR2 proteins were significantly reduced, while the expression of PKA, BDNF, and p-CREB proteins was significantly increased compared to rats undergoing surgery.

It also improved neuronal arrangement and morphology in rats undergoing surgery with dexmedetomidine treatment (35). In another study, the number of doublecortin staining cells in the dg region of the hippocampus, protein, and BDNF gene expression, and p-CREB/CREB and PKA production increased significantly, and the p-MAPK /MAPK ratio decreased significantly (40). In the study of Chen et al., Plasma S100β and NSE levels significantly decreased Caspase-3, pJAK2, and pSTAT3 protein expression (47).

Vitamin-rich carbohydrate: the results of the study of Zou et al. Showed that the use of vitamin-rich carbohydrates before surgery significantly reduces the expression and levels of biomarkers GRP78, eIF2a, Beclin-1, and Bax and significantly increases the level of BCL-2. The result is a reduction in endoplasmic reticulum (ER) stress and neuronal apoptosis, which reduces cognitive dysfunction resulting from surgery (34).

Exendin-4: in the study, a significant decrease in the levels of pro-inflammatory cytokines, marker IBA-1, tau hyperphosphorylation in ser396 and ser199/202, as well as a significant increase in the expression of GLP-1, GLP-1R and p-GSK-3β proteins in the hippocampus and synaptophysin were observed (36).

Methane-rich saline: receiving this treatment in mice who underwent surgery significantly reduces the transcription and expression of pro-inflammatory cytokines such as TNF-α and IL-6. Also, the results of a study by Zhang et al. Show that receiving this treatment can reduce significant cell body-to-cell size ratio and phosphorylation of ERK, JNK, P38, and P65. Receiving this treatment also reduced the activity of IBA-1 markers (22).

Honokiol: in two studies, the effect of this treatment on mice undergoing surgery was investigated. In both studies, neuronal apoptosis, expression levels of IBA-1, IL-1β, mitochondrial ROS, and malondialdehyde were significantly reduced (18,23) and showed a positive effect of Honokiol on the side effects of surgery and anesthesia. Expression levels of LC3-II, Beclin-1, PINK1, Parkin, NLRP3, ASC, Caspase-1, and IL-18 were significantly reduced by receiving Honokiol treatment (23). Expression levels of MCP-1, Ac-SOD2, and cytochrome C levels decreased significantly, while sirt3 expression levels increased significantly and SOD2 expression levels did not change significantly (18).

Ginsenoside Rg1: administration of Ginsenoside Rg1 in mice undergoing surgery significantly increased ATP production, basal mitochondrial respiration and mitochondrial membrane potential, maximal mitochondrial respiratory capacity, and uncoupling, Sirt3 expression and deacetylation activity in these mice increased significantly, while ROS levels decreased significantly (24).

Purmorphamine: the expression of Shh, LC3-II, LC3-II / LC3-I proteins was significantly increased in rats treated with purmorphamine compared to rats that underwent surgery alone, while the expression of P62 was decreased (37).

Siegesbeckia Orientalis: two doses of high (1.5 g / kg) and low (0.75 g / kg) were used in operated mice. The regulation of pro-inflammatory cytokines such as IL-6 and IL-1β was significantly reduced at high doses, while the effect of low doses was not positive and no significant change was achieved. High and low doses did not affect the regulation of IL-8 and TNF-α and no change was observed. The use of high doses of this treatment significantly reduced the phosphorylation of JNK and P65, while its low dose did not affect their phosphorylation. Both doses used significantly reduced tau phosphorylation. The results of this study indicate that low doses may not be very suitable for the treatment of complications of surgery and anesthesia in

contrast to high doses (25).

Mycobacterium vaccine immunization: the results of using this strategy show that regulation of NFKBIA, expression of protein and gene of IL-1β and CD3 mRNA significantly decreased as well as regulation of IL-4, Arginase1, and expression of Foxp3 mRNA significantly increased while this strategy does not affect CD4 mRNA expression (38).

Emulsified form of resveratrol: 5 doses of 80 mg / kg, 60 mg / kg, 40 mg / kg, 20 mg / kg and 2 mg / kg were used for this treatment. Doses of 80 mg/kg, 60 mg/kg, and 40 mg/kg were reduced there were significant levels of IL-1β and TNF-α, while the other two doses did not affect pro-inflammatory cytokines (39).

Nicotine: at a dose of 0.5 mg/kg used in rats undergoing surgery nicotine could significantly reduce the expression of pro-inflammatory cytokines il-1β, TNF-α, HMGB-1, and NF-κB P65, and measurements of BDNF and p-TrkB expression showed a significant postoperative day Increased three days after surgery was not significantly different from rats that underwent surgery alone. Cleaved caspase-3 expression and neuronal apoptosis were also assessed one and three days after surgery and a significant decrease was observed (41).

Nimodipine: in two studies, this treatment was used and the results show that this treatment significantly reduced neuronal apoptosis and the amount of (Ca2+)i in the hippocampus (45, 42). Can and caspase-3 expression (42), Bax expression, and Bax/BCL-2 ratio (46) decreased significantly and BCL-2 mRNA expression also increased significantly (45).

Lipopolysaccharide: if lipopolysaccharide is injected into mice 72 or 24 hours before surgery, it causes the number of IBA-1 markers and the level of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 significantly after Surgery is reduced if the level of pro-inflammatory post-inflammatory cytokines is not significantly different from that in mice that have undergone surgery alone if injected during surgery or 6 hours before surgery. Preoperative lipopolysaccharide was not effective at the level of IL-10 and its level was not significantly different from the group of mice that underwent surgery only (19).

Brilliant Blue G: expression of P2X7 receptors, precursor caspase 1 and p20, and IBA-1 marker levels were significantly decreased in the DG and CA1 regions of the hippocampus.

Hydrogen molecule (H2): in the study of Xin et al., A hydrogen molecule with a concentration of 2% was used to treat and improve the complications of surgery and anesthesia in rats. The results of this study show that the use of H2 can increase caspase-3 activity and cytokine levels. Significantly reduce pro-inflammatory IL-1β, IL-6, and HMGB1 in serum and hippocampus after surgery. H2 did not affect TNF-α level in serum and hippocampus (43).

Hydrogen-rich saline: saline-rich hydrogen at a dose of 10 mg/kg significantly reduced TNF-α and IL-1β levels and NF-κB activity in the hippocampus. The light density of TNF-α and IL-1β was also significantly reduced in the hippocampus (27).

Edaravone: the use of this treatment after abdominal surgery significantly reduced neuronal death and neuroapoptosis in the hippocampus, and also significantly reduced GRP78 and chop expression with edaravone (28).

α7nAchR agonist PHA568487: neuronal apoptosis in the hippocampus, caspase-3 expression, and serum levels of S100β, TNF-α, and il-6 were significantly reduced under the influence of α7nachr agonist PHA568487. The expression of p-Akt and p-GSK3β was also significantly increased, while the treatment used in this study did not affect the total levels of Akt and GSK3β (44).

Hypertonic saline 7/5%: use of this treatment after surgery significantly reduced neuronal apoptosis and (Ca2+)i in the hippocampus, and significantly decreased Bax mRNA expression, and significantly increased BCL-2 mRNA expression (45).

Glycyrrhizin: levels of HMGB1, TLR4, il-1β, TNF-α, BACE1, IL-6, nuclear and cytosolic protein NF-κB in the hippocampus of elderly mice were significantly reduced by the effect of glycyrrhizin after splenectomy, PSD95 expression was also significantly in mice Elderly levels increased significantly but glycyrrhizin had no effect on synapsin I expression (29).

Pyrrolidine dithiocarbamate: the use of Pyrrolidine dithiocarbamate significantly reduced GDNF concentrations in rats undergoing surgery while not affect BDNF concentrations. IBA-1 marker expression was also significantly decreased under the influence of the treatment used (46).

Minocycline: the levels of IL-1β, TNF-α, IFN-γ, IBA-1 were significantly reduced and the levels of IL-4 and il-10 were significantly increased by the dose of 45 mg/kg of minocycline (30).

Deferoxamine: the effects of this drug at a dose of 100 mg/kg were evaluated in two studies and the concentrations of iron, hepcidin, DMT1, malondialdehyde, reactive oxygen species (ROS) in the hippocampus were significantly reduced (31,48). The level of Fpn-1 increased significantly in the study of Li et al. (31) while in the study of Pan et al. It decreased significantly (48). BDNF expression increased significantly and CD68 and TNF-α and IL-1β levels in the hippocampus decreased significantly (31). The expression of ferritin, caspase-3, Bax, integrated optical density and average cell body size, cell body to cell size ratio decreased significantly while the expression of TfR and BCL-2 increased significantly (48).

Conclusion

Postoperative brain injuries are caused by anesthetics and surgery. Postoperative neurological defects can cause cognitive dysfunction (4, 49). The probability of cognitive dysfunction after cardiovascular surgery is between 28 to 100% and after general surgery is usually between 7 to 28% (50-52).

Postoperative brain damage remains a major problem because it can increase mortality among patients. The purpose of this systematic review study, written according to Prism guidelines, is to evaluate the effectiveness of drug strategies to reduce surgical brain damage.

By searching for keywords in databases, we selected studies that met the input criteria after careful review and extracted their information. Findings from these studies show that mice and rats that receive medication before and after surgery can improve neuritis and brain damage compared to mice and rats that receive surgery alone, and therefore can reduce side effects from surgery and anesthetics. For more detailed studies, it is necessary to conduct human studies in this field to be able to comment more confidently on the effect of drugs on side effects after surgery and anesthesia.

Acknowledgment

None.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Abbreviation

NFKBIA: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; FOXP3: forkhead box P3; IL: interleukin; IBA-1: ionized calcium-binding adapter molecule 1; MAPKs: mitogen-activated-protein kinases; MLKs: Mixed-lineage kinases; JNK: c Jun amino-terminal kinase; SYN: synaptophysin; PSD95: postsynaptic density protein 95; KYNA: kynurenic acid; QUIN: quinolinic acid; TNF-α: tumor necrosis factor-α; Aβ: amyloid β-protein; GRP-78: glucose-regulated protein 78; eIF2a: eukaryotic translation initiation factor 2 subunit a; ER: endoplasmic reticulum; GABABR: γ-amino butyric acid-B receptor; PKA: protein kinase A; cAMP: cyclic adenosine monophosphate; CREB: cAMP-response element binding; BDNF: brain-derived neurotrophic factor; LPS: lipopolysaccharide; GLP-1: glucagon-like peptide 1; GLP-1R: glucagon-like peptide 1 receptor; MDA: malondialdehyde; ROS: reactive oxygen species; SIRT3: Sirtuin3; SOD2: superoxide dismutase 2; ATP: Adenosine triphosphate; FOXP3: forkhead box P3; DCX: doublecortin staining; HMGB-1: high mobility group box-1; CaN: Calcineurin; CHOP: CCAAT-enhancer-binding homologous protein; GSK3β: glycogen synthase kinase 3β; p- GSK3β: phosphorylated glycogen synthase kinase 3β; BACE1 Beta-secretase 1; TLR4: Toll-like receptor 4; GDNF: glial cell-derived neurotrophic factor; BrdU: 5′-bromo-2′-deoxyuridine; NeuN: neuronal nuclei, Bcl-2: B cell lymphoma 2; Bax: Bcl-2 associated X protein; Fpn1: ferroportin 1; DMT1: divalent metal transporter 1; TfR: transferrin receptor..

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed regarding participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in the systematic review, and, if applicable, included in the meta-analysis).	2-3
Data collection process	10	Describe the method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing the risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, the difference in means).	-
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of the risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3
Risk of bias within studies	19	Present data on the risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	3-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of the risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policymakers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	-
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., the supply of data); the role of funders for the systematic review.	-

The PRISMA statement is based on the model from Moher, et al. (53). For more information, visit **www.prisma-statement.org**.

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