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Anaesthetic-Related Neuroprotection
Intravenous or Inhalational Agents?

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Abstract

In designing the anaesthetic plan for patients undergoing surgery, the choice of anaesthetic agent may often appear irrelevant and the best results obtained by the use of a technique or a drug with which the anaesthesia care provider is familiar. Nevertheless, in those surgical procedures (cardiopulmonary bypass, carotid surgery and cerebral aneurysm surgery) and clinical situations (subarachnoid haemorrhage, stroke, brain trauma and post-cardiac arrest resuscitation) where protecting the CNS is a priority, the choice of anaesthetic drug assumes a fundamental role. Treating patients with a neuroprotective agent may be a consideration in improving overall neurological outcome. Therefore, a clear understanding of the relative degree of protection provided by various agents becomes essential in deciding on the most appropriate anaesthetic treatment geared to these objectives.

This article surveys the current literature on the effects of the most commonly used anaesthetic drugs (volatile and gaseous inhalation, and intravenous agents) with regard to their role in neuroprotection. A systematic search was performed in the MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINHAL®) and Cochrane Library databases using the following keywords: 'brain' (with the limits 'newborn' or 'infant' or 'child' or 'neonate' or 'neonatal' or 'animals') AND 'neurodegeneration' or 'apoptosis' or 'toxicity' or 'neuroprotection' in combination with individual drug names ('halothane', 'isoflurane', 'desflurane', 'sevoflurane', 'nitrous oxide', 'xenon', 'barbiturates', 'thiopental', 'propofol', 'ketamine'). Over 600 abstracts for articles published from January 1980 to April 2010, including studies in animals, humans and *in vitro*, were examined, but just over 100 of them were considered and reviewed for quality.

Taken as a whole, the available data appear to indicate that anaesthetic drugs such as barbiturates, propofol, xenon and most volatile anaesthetics (halothane, isoflurane, desflurane, sevoflurane) show neuroprotective effects that protect cerebral tissue from adverse events – such as apoptosis, degeneration, inflammation and energy failure – caused by chronic neurodegenerative diseases, ischaemia, stroke or nervous system trauma. Nevertheless, in several studies, the administration of gaseous, volatile and intravenous anaesthetics (especially isoflurane and ketamine) was also associated with dose-dependent and exposure time-dependent neurodegenerative effects in the developing animal brain. At present, available experimental data do not support the selection of any one anaesthetic agent over the others. Furthermore, the

relative benefit of one anaesthetic versus another, with regard to neuroprotective potential, is unlikely to form a rational basis for choice. Each drug has some undesirable adverse effects that, together with the patient's medical and surgical history, appear to be decisive in choosing the most suitable anaesthetic agent for a specific situation. Moreover, it is important to highlight that many of the studies in the literature have been conducted in animals or *in vitro*; hence, results and conclusions of most of them may not be directly applied to the clinical setting. For these reasons, and given the serious implications for public health, we believe that further investigation – geared mainly to clarifying the complex interactions between anaesthetic drug actions and specific mechanisms involved in brain injury, within a setting as close as possible to the clinical situation – is imperative.

The term 'neuroprotection' refers to a collection of mechanisms and strategies used to protect neural tissue from cellular events (such as apoptosis, degeneration, inflammation and energy failure) related to chronic neurodegenerative diseases (e.g. Parkinson's disease, Alzheimer's disease and multiple sclerosis) or as a result of acute disorders (e.g. ischaemia, stroke or trauma).[1] CNS neurons are extremely sensitive to any impairment of substrate delivery, especially oxygen-glucose deprivation, which represents one of the leading causes of irreversible brain damage.[2]

Since many of these insults may occur during the perioperative period,[3] protecting the brain of patients undergoing surgery represents one of the most important concerns for anaesthetists, i.e. the choice of the most appropriate anaesthetic treatment geared to these objectives.

In the last few decades, intravenous anaesthetic-based anaesthesia has been extensively used, becoming the treatment of choice during many surgical procedures where neuroprotection is a major concern for anaesthesiologists (such as neurosurgery, carotid endarterectomy and open-heart procedures), and almost completely replacing inhalational anaesthesia.

This article surveys available, up-to-date information on the effects of the most commonly used anaesthetic agents in terms of neuroprotection and, in particular, compares the drugs used in the two different anaesthetic techniques, highlighting if the choice of replacing volatile inhalation with intravenous anaesthesia is supported by scientific evidence in the literature. The following question ''What are the neuroprotective effects of the most common anaesthetic drugs?'' was formulated and used as a starting point for deriving search terms, as well as inclusion criteria, for retrieving articles. More specifically, the name of each anaesthetic drug ('halothane', 'isoflurane', 'desflurane', 'sevoflurane', 'nitrous oxide', 'xenon', 'barbiturates', 'thiopental', 'propofol', 'ketamine') in combination with terms such as 'brain' (with the limits 'newborn' or 'infant' or 'child' or 'neonate' or 'neonatal' or 'animals') AND 'neurodegeneration' or 'apoptosis' or 'toxicity' or 'neuroprotection' was used. Owing to the medical nature of the question, the search was confined to three databases: the Cochrane Library, MEDLINE accessed through PubMed and the Cumulative Index to Nursing and Allied Health Literature (CINAHL®). Over 600 abstracts, published from January 1980 to April 2010, and including studies in animals, humans and *in vitro* were found. After a careful screening process, just over 100 of these articles were considered and reviewed for quality. The screening process took into account factors such as language, publication data, availability of an abstract and full text, relevance, duplication of data and study type.

1. Anaesthetics and Neuroprotection

On the basis of the modality of administration, anaesthetic agents can be divided into two subclasses: those delivered by inhalation and those delivered intravenously. As well as gaseous nitrous

oxide and xenon, the former includes the volatile anaesthetic agents halothane, isoflurane, desflurane and sevoflurane. The latter includes thiopental sodium and other barbiturates, propofol and ketamine.

1.1 Volatile Inhalation Anaesthetic Agents

Volatile inhalational anaesthetics may play an important role during major surgical procedures. Several studies have demonstrated some degree of neuroprotective effect, highlighting how these agents may influence brain metabolism and neurological outcome (reviewed by Miura and Amagasa[4]). Short-term neuroprotection (<1 week post-ischaemia) in cerebral ischaemia has been reported in several experimental animal studies, whereas long-term neuroprotection (≥1 week post-ischaemia) remains controversial.[5] These data suggest that mechanisms related to the neuroprotective effect of volatile anaesthetic agents include activation of adenosine triphosphate (ATP)-dependent potassium channels, upregulation of nitric oxide synthase, reduction of excitotoxic stressors and cerebral metabolic rate, augmentation of peri-ischaemic cerebral blood flow and upregulation of antiapoptotic factors, including mitogen-activated protein kinases.[5]

1.1.1 Halothane

Halothane has been generally replaced in clinical practice by other volatile anaesthetics because of its potential hepatotoxicity, which is associated with a high mortality rate. Nevertheless, it is still employed in several developing countries.[6]

Investigations into the neuroprotective effects of this anaesthetic agent are scarce. Nakao and colleagues[7] demonstrated that halothane – like other anaesthetics, such as isoflurane, barbiturates and benzodiazepines
damage caused by NMDA receptor antagonists in the rodent posterior cingulate and retrosplenial cortices, probably through GABA
tivation. The neuroprotective effects of halothane have been evaluated in experimental models of global and focal brain ischaemia in gerbils and rats.[8,9] In particular, in the former model, it has been shown that halothane attenuates the severity of ischaemic depolarization, neuronal damage and extracellular glutamate level, but less effectively than thiopental and propofol.[9] Haelewyn et al.[8] demonstrated that, although halothane provides protection against focal cerebral ischaemia, its neuroprotective effect is less than that conferred by desflurane. Furthermore, in rats, prior exposure to halothane, as well as isoflurane, desflurane and sevoflurane, has been shown to induce a neuroprotection phenomenon (called preconditioning) in a concentration-dependent manner.[10] The continued administration of halothane decreases oxygen-glucose deprivation-induced neuronal apoptosis in neuronal cortical cell cultures prepared from newborn rats *in vitro*.[11]

No prospective studies have examined the effects of halothane exposure early in life on neuronal structure and neurocognitive outcome.[12,13] Transient behavioural abnormalities, such as fear of strangers, temper tantrums, attention seeking, sleep disturbance, enuresis and anxiety, have been described after paediatric halothane anaesthesia.[13-17] As shown by laboratory experiments, prenatal halothane exposure in clinical doses between gestational days 3 and 17 consistently led to learning impairment in adulthood, whereas subclinical doses decreased synaptic density, but lacked consistent neurocognitive dysfunction.[13,18,19]

1.1.2 Isoflurane

Isoflurane is a volatile inhalational anaesthetic introduced several decades ago, but still widely used in clinical practice. Similarly to other volatile inhalational anaesthetics, it exhibits neuroprotective effects, inducing a concentration-dependent preconditioning when used prior to exposure.[10] In particular, isoflurane preconditioning reduces Purkinje cell death in an *in vitro* model of rat cerebellar ischaemia,[20] reduces glutamate receptor overactivation-induced Purkinje neuronal injury in the rat cerebellum,[21] improves long-term neurological outcome after brain ischaemia in rats,[22] inhibits isoflurane-induced neurotoxicity[23] and activates hypoxia inducible factor-1α, inducible nitric oxide synthase and extracellular signal-related kinases 1 and 2, protecting against

oxygen-glucose deprivation neuronal injury in rats.[24] Moreover, as shown by Xiong et al.,[25] preconditioning with this drug produces dose-dependent neuroprotection after focal cerebral ischaemia in rats, suggesting that ischaemic tolerance induced by isoflurane depends on activation of ATP-regulated potassium channels. The administration of isoflurane during reperfusion after oxygen-glucose deprivation or brain ischaemia also reduces brain injury in rats.[26] Isoflurane also improves neurological outcome after incomplete cerebral ischaemia in rats.[27] Furthermore, as described for halothane, the continued administration of this drug decreases oxygen-glucose deprivation-induced neuronal apoptosis in neuronal cortical cell cultures prepared from newborn rats *in vitro*.[11]

The effects of isoflurane, combined with other agents such as estradiol or z-IETD-fmk, have also been investigated.[28,29] Wang et al.[29] demonstrated that the use of estradiol attenuates the neuroprotective benefits of isoflurane preconditioning in ischaemic mouse brain. In the case of z-IETD-fmk, experimental evidence shows that the neuroprotective efficacy of isoflurane in rats subjected to focal cerebral ischaemia can be prolonged with the administration of this specific inhibitor of caspase 8.[28] Finally, in a recent study, Sasaoka et al.[30] highlighted how isoflurane exerts a short-term, but not a long-term, preconditioning effect in neonatal rats exposed to hypoxic-ischaemic neuronal injury.

However, contrary to these neuroprotective effects, isoflurane has been linked to apoptotic neurodegeneration in neonatal rhesus macaques and newborn rats, mice, guinea pigs and piglets, with most data being available in 7-day-old mice or rats.[12,13,31-33] In rats, a 6-hour exposure to an anaesthetic combination of isoflurane, midazolam and nitrous oxide has been demonstrated to induce widespread apoptotic neurodegeneration in newborn animals, followed by impairment in learning and memory retention tests later in adulthood.[34,35] Stratmann et al.[36,37] indicate that isoflurane, when administered for 4 hours as a single anaesthetic drug, provokes brain cell death, altering fear conditioning and spatial learning in adulthood. Exposure to isoflurane for 1 hour, instead, is not sufficient to cause brain cell death.[36,37] Experimental data from another research group demonstrate that exposure to subminimum alveolar concentrations of isoflurane for 1 or more hours also triggers neuroapoptosis in the infant mouse brain.[38] All conditions tested (isoflurane at 0.75% for 4 hours, 1.5% for 2 hours, 2.0% for 1 hour), in fact, triggered a statistically significant increase in neuroapoptosis compared with the rate of spontaneous apoptosis in littermate controls.[38] In humans, although anecdotal data suggest at least transient neurological sequelae after prolonged exposure, no studies have been completed examining the long-term effects of isoflurane on the developing brain.[12,13]

1.1.3 Desflurane

Desflurane, a recently introduced volatile anaesthetic drug, has a low blood/gas solubility coefficient that allows rapid changes in anaesthesia level.[39] It is generally used in anaesthesia to facilitate rapid emergence. A faster recovery following desflurane may in fact be desirable, especially after long surgical procedures, enabling the patient's full cooperation, and facilitating early diagnosis of any potential neurological deficit.[40]

The cerebral protective effects of this anaesthetic agent have been investigated, *in vitro*, by Wise-Faberowski and colleagues.[41] In particular, they demonstrated how desflurane leads to an extreme reduction (up to 98%) of neuronal cell death related to oxygen-glucose deprivation, regardless of concentration.[41] Haelewyn et al.[8] and Erdem et al.[42] analysed the effects of desflurane on focal or incomplete cerebral ischaemia in rats. In both studies, desflurane induced neuroprotection in a measure greater than that conferred by halothane.[8] Moreover, the use of this volatile anaesthetic, in rats and newborn pigs, improves neurological outcome both after incomplete cerebral ischaemia[27] and following low-flow cardiopulmonary bypass,[43] protecting the developing brain and inducing less functional disability and less histological damage.[12,13,27] Finally, studies in humans have demonstrated that a desflurane-based treatment for cerebral

protection increases brain tissue oxygenation by inhibiting ischaemic lactic acidosis and pH reduction.[1,44]

1.1.4 Sevoflurane

Sevoflurane is currently considered the volatile inhalational agent of choice in anaesthesia and it is widely used in neuroanaesthesia. Similarly to desflurane, *in vitro* it significantly reduces oxygen-glucose deprivation-induced neuronal cell death[41,45] and provides preconditioning in a concentration-dependent manner when administered prior to exposure,[10] and in the animal model shows cerebral protective effects when given after ischaemia.[42] Used alone or in combination with xenon, sevoflurane may also be used to guarantee long-lasting neuroprotection against neuronal injury after an unpredicted asphyxia in the perinatal period.[46] Preconditioning with sevoflurane, or with the combination of xenon and sevoflurane, results in long-term functional neuroprotection, associated with enhanced phosphorylated cyclic adenosine monophosphate response element binding protein signalling.[46] In particular, using an *in vivo* model of global cerebral ischaemia in rats, Payne et al.[47] have shown that sevoflurane provides early and late preconditioning against ischaemic neuronal injury. A recent study[48] more specifically demonstrated that sevoflurane preconditioning can induce delayed neuroprotection against focal cerebral ischaemia in rats by downregulating tumour necrosis factor-α, interleukin-1β protein and messenger RNA expression. The role of glutamate and reactive oxygen species in sevoflurane-mediated neuroprotection has been investigated, *in vitro*, by Canas and colleagues,[49] who demonstrated that sevoflurane has a neuroprotective effect after ischaemia/re-oxygenation. This beneficial effect may be explained, at least in part, by sevoflurane-induced anti-excitotoxic properties during oxygen-glucose deprivation and by a sevoflurane-induced decrease in reactive oxygen species generation during re-oxygenation.[49]

Finally, sevoflurane anaesthesia during surgery in young children has been associated with postoperative behavioural changes, such as increased temper tantrums, sleep disturbance and loss of appetite.[12-15] However, contrasting these deleterious effects of sevoflurane, preliminary data in neonatal mice suggest that sevoflurane does not cause apoptotic neurodegeneration in the developing brain following clinically relevant exposure times and concentrations.[50,51]

1.2 Gaseous Inhalation Anaesthetic Agents

Currently, anaesthetics are thought to produce anaesthesia via interaction with receptor targets, most commonly $GABA_A$ receptors and possibly other receptors, such as the NMDA subtype of the glutamate receptor,[52] which potentiate inhibitory neurotransmission and inhibit excitatory neurotransmission, respectively.[53] Nitrous oxide and xenon are anaesthetic gases that have a distinct pharmacological profile. Whereas the molecular basis for their anaesthetic actions remains unclear, they behave very differently to most other general anaesthetics in that they have little or no effect on $GABA_A$ receptors, yet strongly inhibit NMDA receptors.[54,55] For these reasons, they are often grouped into a specific class of anaesthetics with effects on NMDA receptors (particularly those containing the NR1a/NR2D subunit) but not on $GABA_A$ receptors.[56] Even nicotinic acetylcholine receptors (nAChR), especially those composed of β_2-subunits, have been indicated as potential targets for nitrous oxide and xenon.[55] In fact, nAChR were inhibited by gaseous anaesthetics with different sensitivity between $\alpha_4\beta_2$ and $\alpha_4\beta_4$ receptors: for example, nitrous oxide inhibited $\alpha_4\beta_2$ receptors by 39%, and $\alpha_4\beta_4$ receptors by 7%.[55] Finally, certain members of the two-pore-domain potassium channel superfamily (TREK and TASK), which modulate neuronal excitability, may also represent an important new target for these gaseous anaesthetics.[53,54] Clinically relevant concentrations of nitrous oxide and xenon, in fact, have been shown to markedly activate TREK-1, but not TASK-3, channels.[53,54]

1.2.1 Nitrous Oxide

Nitrous oxide is a weak anaesthetic agent and, for this reason, is usually given in combination with more powerful volatile anaesthetic drugs,

such as sevoflurane, desflurane, isoflurane or halothane. Preliminary studies have shown the neuroprotective action of nitrous oxide, especially on NMDA-induced neuronal injury.[57] However, because of possible neurotoxic and proneurotoxic effects (obtained under particular conditions) and its poor performance at anaesthetic concentrations, little research has been carried out on the neuroprotective effects of this anaesthetic.[58] As demonstrated by studies performed in animal models, nitrous oxide seems to offer neuroprotective properties, especially when administered alone at non-anaesthetic doses, reducing excitotoxic neuronal death and ischaemic brain damage in the cortex when given after NMDA injection and occlusion of the middle cerebral artery, respectively.[57-61] For example, in rats subjected to transient cerebral ischaemia, nitrous oxide at 50% by volume offers full neuroprotection at both the histological and neurological outcome levels when administered up to 2 hours, but not 3 hours, after ischaemia onset.[58]

Nevertheless, cerebral protection induced by other anaesthetics appears to be adversely affected by coadministration of nitrous oxide.[1] The neuroprotective efficacy of isoflurane against cerebral ischaemia or stroke in rats, for example, is significantly altered by coadministration of nitrous oxide and vice versa.[4,62] Similarly, while barbiturates showed limited efficacy as neuroprotective agents in experimental animal studies that used nitrous oxide as part of the anaesthetic strategy, they appear efficacious in those studies that did not use nitrous oxide.[1]

In relation to the developing brain, case studies in neonates exposed to nitrous oxide *in utero* during the third trimester of pregnancy[63] or during caesarean delivery[64]
neurological sequelae, such as increased muscle tone, habituation to sound, resistance to cuddle and fewer smiles, without long-term follow-up.
animal studies, no significant increase in apoptotic neurodegeneration was found in either neonatal rats treated with 50%, 75% or 150% (in a hyperbaric chamber) nitrous oxide for 6 hours,[34] or in neonatal rats exposed to 75% nitrous oxide for 6 hours.[32] However, *in vivo* administration of nitrous oxide at a dose of 75% exacerbated neuroapoptosis caused by isoflurane 0.75%.[13,32] Finally, some more or less recent studies[65-67] indicate that post-ischaemic nitrous oxide does not inhibit tissue-type plasminogen activator-induced brain haemorrhages and disruption of the blood-brain barrier, and does not reduce ischaemic brain damage in a similar amplitude to post-ischaemic xenon.[65] Therefore, particular caution in using nitrous oxide is suggested.

1.2.2 Xenon

Xenon is an inert gaseous anaesthetic with NMDA receptor-antagonist properties, which exhibits neuroprotective effects, similarly to other anaesthetics (such as nitrous oxide and ketamine), and with similar antagonistic properties. But, unlike these agents, xenon is devoid of both neurotoxicity and clinically significant adverse haemodynamic properties.[53,68-71] Rather, xenon seems to be a nonspecific channel blocker: it antagonizes not only NMDA receptors, but also α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate receptors in cortical neurons, as well as glutamate R6-type receptors expressed in SH-SY5Y cells.[72]

In terms of neuroprotection, the administration of this drug has been associated with reduction of cardiopulmonary bypass-induced neurological and neurocognitive dysfunctions in rats,[73] and cardiac arrest-induced brain injury in pigs.[74] The neuroprotective effects of xenon during cardiopulmonary bypass seem to be independent of effects on the inflammatory response to cardiopulmonary bypass.[75] In the case of cardiac arrest, xenon confers neurohistopathological protection, which translates into transiently improved functional outcome.[76] Other animal studies have also demonstrated that the use of xenon attenuates ischaemia-induced brain damage *in vivo* after occlusion of the middle cerebral artery, showing how it is able to reduce ischaemic brain damage in the striatum, a subcortical structure known to be resistant to neuroprotective interventions, and to improve both functional and histological outcome.[59,61,77] When administered after hypoxia-ischaemia in neonatal rats, treatment with xenon provides short-term neuroprotection,

without other neurotoxic effects and with minimal adverse effects. This suggests that xenon is an ideal candidate for the treatment of human perinatal hypoxia-ischaemia.[78] Xenon also attenuates ongoing neuronal injury in *in vitro* and *in vivo* models of hypoxic-ischaemic injury when administered during, after and also before the insult.[79]

In recent years, the application of xenon, alone or in combination with other anaesthetic agents or techniques, has been analysed in a large number of studies. David and colleagues,[65] for example, have investigated whether xenon may alter the catalytic efficiency of alteplase, a serine protease that is the only currently approved therapy for acute ischaemic stroke. Results indicate that intra-ischaemic xenon should be avoided due to the risk of inhibiting the benefits of alteplase therapy, while post-ischaemic xenon could constitute a gold standard because of its unique neuroprotective and antiproteolytic (antihaemorrhaging) properties, allowing blockade of both excitotoxic processes and alteplase toxicity.[65] Luo et al.[46] have investigated the use of xenon and sevoflurane, independently or in combination, to attenuate perinatal injury. The authors demonstrated that preconditioning with these agents provides long-lasting neuroprotection in a perinatal hypoxic-ischaemic model and may represent a viable method to prevent neuronal injury after an unpredicted asphyxial event occurring in the perinatal period.[46]

The effects of xenon and helium have been studied by Coburn et al.,[80] in an *in vitro* model of traumatic brain injury at normal and elevated pressures, and under both normothermic and hypothermic conditions. They demonstrated that low pressures of both helium and xenon were effective neuroprotectants when applied in addition to 1 atmosphere of air, while both gases were effective at normal pressure when they replaced nitrogen in a gas mixture.
highlight that helium, under certain conditions of gas temperature, can provide neuroprotection against acute ischaemic stroke *in vivo* and, on the basis of these findings, they suggest that combining helium with xenon may help in reducing the excessive cost of treatment with xenon while ensuring the same levels of neuroprotection. In fact, although closed xenon delivery systems for humans are now being developed, the widespread clinical use of xenon remains strongly limited by its low availability and excessive cost of production.[58] Furthermore, xenon/hypothermia neuroprotection regimens have been investigated by Ma et al.,[82] who suggested that low (subanaesthetic) concentrations of xenon, in combination with mild hypothermia, might provide a safe, effective therapy for perinatal asphyxia. Hypothermia can also be used to improve the length of neuroprotection after neonatal hypoxia-ischaemia.[83,84]

The effects of xenon on neuronal structure and neurocognitive performance have not been studied in young children.[12,13] In animals studies, it has been observed that exposure to xenon did not increase apoptotic neuronal death in neonatal rats but, rather, it attenuated the neurotoxic effects of isoflurane and nitrous oxide.[32,85]

1.3 Intravenous Anaesthetic Agents

1.3.1 Barbiturates

Barbiturates or barbituric acid-derived drugs act on the CNS as depressants, producing a wide spectrum of effects ranging from mild sedation to anaesthesia. In numerous experimental models of ischaemia, both *in vitro* and *in vivo*, these drugs have exhibited significant protective properties against ischaemic injury.[86,87] Also, earlier works by Safar's group have suggested that barbiturates could be neuroprotective,[88] but their later research did not support the use of thiopental for brain resuscitation after cardiac arrest.[89,90]

Preliminary studies of neuroprotection suggested that barbiturate-associated protection was mediated by a reduced metabolic demand.[91] Nevertheless, Schmid-Elsaesser et al.[92] showed that other mechanisms than cerebral metabolic rate reduction might contribute to the beneficial effects of these drugs. In particular, facilitation of protein synthesis, GABAergic activity and antioxidant activity are all factors that may play a role in the neuroprotective effects of barbiturates.[93] Also, the adenosine-induced depression of excitatory synaptic transmissions probably contributes to these mechanisms.[94] Actually, the accumulation of endogenous adenosine in the

extracellular space, facilitated by barbiturates through the inhibition of uptake by adenosine transporters, depresses excitatory synaptic transmission by decreasing transmitter release. This, in turn, depresses postsynaptic sensitivity and inhibits neuronal excitability through adenosine A_1 receptors and the related adenosine neuromodulatory system.[94] Moreover, since ATP-sensitive potassium channels are thought to be involved in neuroprotection against cell damage during hypoxia, ischaemia and excitotoxicity through a process of neuron hyperpolarization and excitability reduction, the effects of barbiturates on this kind of neuronal channel have also been investigated. Ohtsuka and colleagues[95] demonstrated that barbiturates at high concentrations, but not at clinically relevant concentrations, inhibit ATP-sensitive potassium channels activated by intracellular ATP depletion in the rat substantia nigra.

Pentobarbital and thiopental are some of the most frequently used barbiturates in clinical practice. The former appears effective in terms of controlling refractory intracranial hypertension in patients with severe traumatic brain injury,[96] and provides behavioural neuroprotection against kainic acid-induced neurotoxicity.[97] The latter provides maximal neuroprotection on cortical cultures exposed to prolonged hypoxic episodes when administered in combination with hypothermia.[98]

Current evidence for the adverse neurological effects of barbiturates on the developing human brain is limited to case reports, usually attributed to withdrawal symptoms, and long-term neurological follow-up is lacking.[13] In animal studies, however, barbiturates seem to be associated with a dose-dependent neurodegeneration. In newborn rats, in fact, increases in neuronal degeneration have been observed in rat pups after injections of pentobarbital 5–10 mg
40–100 mg/kg,[99,100] while phenobarbital in lower doses (between 20 and 30 mg
neurodegeneration.[13]

Thiopental is a rapid-onset, short-acting barbiturate anaesthetic agent. It is commonly used as a neuroprotective agent and its pharmacological properties have been widely investigated. In the late 1990s, Guo et al.[101] and Zarchin et al.[102] demonstrated, independently, that thiopental induces cerebral protection against ischaemia in dogs and gerbils, respectively. Furthermore, Hoffman and colleagues[44] demonstrated that thiopental, as well as desflurane, increases brain tissue oxygenation, inhibiting ischaemic lactic acidosis and decreasing pH when administered for brain protection during brain artery occlusion in patients undergoing craniotomies for cerebrovascular surgery. In recent years, it has also been shown that, in animal models, thiopental provides a greater suppressive effect on neuronal injury during identical duration of ischaemic depolarization compared with propofol.[9] Moreover, according to Xue et al.,[103] thiopental guarantees neuroprotective effects against oxygen-glucose deprivation injury in rat cerebral cortical slices, while a high concentration of propofol augments its effect. On the other hand, propofol, but not thiopental, provides neuroprotective effects against reperfusion-induced injury in rats subjected to focal cerebral ischaemia.[104] Both these GABA-mimetic anaesthetics (propofol and thiopental) protect against the irreversible neurodegenerative reaction induced by the powerful NMDA antagonist, dizocilpine (MK-801).[105] Additionally, thiopental attenuates the decrease in hippocampal phosphorylated focal adhesion kinase (pp125FAK) content induced by oxygen-glucose deprivation.[106] The use of thiopental, in combination with reduced doses of ketamine, has been suggested by Shibuta et al.[107] to increase protection of cerebral cortical neurons from ischaemia and NMDA-induced neurotoxicity. The effectiveness of thiopental in terms of control of refractory intracranial hypertension in patients with severe traumatic brain injury has been investigated, also to analyse the adverse effects of treatment with anaesthetics.[96] Notwithstanding the fact that results should be interpreted with caution because of the imbalance in pathological characteristics of patients and different dosages employed, this study demonstrated that thiopental is more effective than other barbiturates, including pentobarbital.[96] Finally, neonatal exposure to thiopental in doses between 5 and 25 mg/kg did not lead to an increase in neurodegeneration or long-term behavioural or learning impairments in mice.[12,13,108]

1.3.2 Propofol

Propofol is a phenolic derivative that is structurally unrelated to other sedative hypnotic agents. It is an intravenous agent widely used for the induction of general anaesthesia in adult and paediatric patients older than 3 years of age; maintenance of general anaesthesia in adults and children older than 2 months of age; and intensive care unit sedation for mechanically ventilated adults. The pharmacokinetic profile of propofol is characterized by rapid onset and short duration of action which, together with its stress control and amnesic properties, makes it an ideal hypnotic agent for use during surgical procedures. Propofol is a global CNS depressant. It activates $GABA_A$ receptors directly, inhibits the NMDA receptor and modulates calcium influx through slow calcium ion channels, and has demonstrated neuroprotective effects related to a decrease in cerebral metabolic rate for oxygen, and to other pharmacological properties.[109,110] Ito et al.[111] demonstrated that propofol activates $GABA_A$ receptors and significantly reduces neuronal damage induced by forebrain ischaemia.[111] Grasshoff and Gillessen[112] observed that, in the presence of high propofol concentrations, the NMDA receptor-mediated calcium increase is inhibited and this contributes to the neuroprotective effects of this drug.

In general, the effects of propofol on cerebral ischaemia have been investigated in many *in vivo* and *in vitro* experimental models. During ischaemic depolarization in gerbils, propofol has been reported as having a lesser suppressive effect on neuronal injury than thiopental.[9] In rat organotypic hippocampal slices exposed to oxygen-glucose deprivation, propofol, administered at clinically relevant concentrations, provides neuroprotective effects when present in the incubation medium during oxygen-glucose deprivation and during the following 24-hour recovery period.
In pheochromocytoma cell line 12 (PC12) cells, the propofol protection effect against oxygen-glucose deprivation-induced cell damage is enhanced when edetic acid (EDTA) is added.[110,114] On the other hand, high concentrations of propofol increase oxygen-glucose deprivation-induced injury in rat cerebral cortical slices.[103]

Experimental studies in traumatic brain injury are limited and less encouraging.[115] Moreover, some animal studies point to the dose-dependent neurodegenerative properties of propofol in the developing rat brain.[13,50] Cattano and colleagues[116] demonstrated that subanaesthetic doses (one-quarter the dose required for surgical anaesthesia) of propofol induce neuroapoptosis in the infant mouse brain, while Pesić et al.[117] provide direct experimental evidence that the anaesthetic dose (25 mg/kg) of propofol induces complex changes that are accompanied by cell death in the cortex and thalamus of the developing rat brain. Therefore, propofol cannot be indicated as an established clinical neuroprotective agent *per se*, but it might play an important role in a global strategy for the treatment of injury of the brain that includes preservation of cerebral perfusion, temperature control, prevention of infections and tight control of serum glucose levels.[115]

1.3.3 Ketamine

Ketamine is a non-competitive antagonist of NMDA receptors that has well documented neuroprotective effects against ischaemic brain injury and glutamate-induced brain injury. Initial evidence for ketamine neuroprotective effects derives from cell culture studies demonstrating that ketamine administration: (i) increases neuronal and astroglial viability; (ii) preserves cellular morphology; (iii) reduces cell swelling subsequent to anoxia-hypoxia or glutamate injury; (iv) preserves the cellular energy status after ischaemic insults; and (v) preserves ATP production.[118] Further studies demonstrated that the use of ketamine attenuates the impaired cognitive behaviour resulting from pain-induced cell death in the cortical and hippocampal fields of neonatal rats,[119] and that ketamine has neuroprotective effects against oxygen-glucose deprivation injury in rat cerebral cortical slices.[103] In addition, it has been reported that ketamine inhibits endotoxin-induced nuclear factor κB expression in brain cells *in vivo* and *in vitro,* suggesting that this may have implications in the neuroprotective effects of ketamine reported by other investigators.[120] Similarly, the inhibition

of transcription factor c-Jun activity seems to be involved in the neuroprotective effects of this anaesthetic against glutamate-induced injury in neuronal PC12 cells.[121]

Nevertheless, contrary to the neuroprotective effects described above, intra-ischaemic ketamine did not provide neuroprotection in an experimental model of spinal cord ischaemia.[122] Moreover, recent experimental data obtained in developing animals point to a dose-dependent and exposure time-dependent neurodegenerative effect.[12,13] In their studies Zou and colleagues,[123,124] for example, demonstrated that no significant neurotoxic effects occurred if the anaesthesia duration was 3 hours, while ketamine infusions for either 9 or 24 hours significantly increased neuronal cell death in layers II and III of the frontal cortex in the developing monkey brain and in the developing rat brain. Similarly, no significant neurotoxic effects were detected in layers II or III of the frontal cortex of rats administered one, three or six injections of ketamine 5 or 10 mg/kg, whereas in rats administered six injections of ketamine 20 mg/kg, a significant increase in the number of caspase-3- and Fluoro-Jade C-positive neuronal cells was observed in the frontal cortex.[124] Soriano et al.[125] also confirmed these findings, highlighting how ketamine induces aberrant cell cycle re-entry, leading to apoptotic cell death in the developing rat brain. No information is available regarding the effects of clinical doses of ketamine on neuronal structure or neurocognitive functions in young children.[13] Finally, although ketamine shows great neuroprotective potential, several unfavourable effects make it very unsuitable in patients with cerebral ischaemia.[107]

2. Intravenous versus Inhalational Anaesthesia: Some Considerations about Potential Neuroprotective Effects

On the basis of the current knowledge on the neuroprotective properties of individual anaesthetic agents, the next essential step is understanding the appropriateness of each single agent in clinical practice, especially in the context of the anaesthesiological protocol performed. From this point of view, several experimental studies have compared the neuroprotection offered by inhalational and intravenous anaesthetics. Hans and Bonhomme[126] demonstrated that, in patients with brain tumour undergoing craniotomy, propofol intravenous anaesthesia was associated with lower intracranial pressure and cerebral swelling than inhalation anaesthesia, also providing excellent and predictable recovery conditions, as well as minimal postoperative adverse effects (a lower incidence of nausea and vomiting). During cardiopulmonary bypass, however, propofol appears to offer no advantages over isoflurane-based anaesthesia, especially with regard to cerebral protection: after coronary artery bypass grafting, no modifications to neuropsychological outcome have been reported with either anaesthetic.[127] Similarly, in their study on the comparison of the effects of seven anaesthetic agents on outcome after experimental traumatic brain injury in adult male rats, Statler and colleagues[128] demonstrated that the early, post-traumatic brain injury use of isoflurane, despite practical logistical issues, may be more neuroprotective than other commonly used sedatives or analgesics (diazepam, fentanyl, ketamine, morphine, pentobarbital and propofol). In particular, they observed that rats treated with isoflurane had the best cognitive recovery ($p < 0.05$) and hippocampal neuronal survival ($p < 0.05$). Conversely, rats treated with ketamine had the greatest hippocampal neuronal death ($p < 0.05$). Morphine or propofol were associated with the poorest motor function score on post-trauma days 1–5 ($p < 0.05$).[128]

Compared with propofol, the volatile anaesthetic sevoflurane also decreases cerebral blood flow to a lesser extent, does not increase intracranial pressure (propofol decreases it), while cerebral metabolism is suppressed to the same degree.[129] Kobayashi et al.[9] investigated, in gerbils, the neuroprotective effects against brain ischaemia of propofol and thiopental and compared these two anaesthetics with halothane. In particular, they reported that duration of ischaemic depolarization is equally reduced with thiopental and propofol as compared with halothane; that the severity of neuronal damage, with identical

duration of ischaemic depolarization, is more attenuated by thiopental than propofol; and that maximum glutamate levels are significantly reduced with both anaesthetics rather than with halothane.[9] Chen et al.[104] also analysed the effects of propofol, thiopental and midazolam on outcome in focal cerebral ischaemia-reperfusion, highlighting how propofol and midazolam, but not thiopental, provide protective effects against reperfusion-induced injury in rats subjected to this insult.

Therefore, in general, it is possible to assert that inhalational and intravenous anaesthetic agents, obviously with some minor exceptions, might play an important role in terms of neuroprotection during surgical procedures. Nevertheless, data seem to be insufficient to recommend any specific anaesthetic agent as the optimal neuroprotective agent. In current clinical practice, propofol is largely used in neuroanaesthesia both for its neuroprotective profile and for several advantages it offers, including control of intracranial hypertension, which allows the surgeon to operate under safe, optimal conditions. According to experimental data reported above, in patients with reduced intracranial elastance caused by space-occupying lesions, with elevated intracranial pressure or complex surgical approaches, propofol seems to be the agent of first choice, while in neurosurgical patients with normal intracranial pressure who are at risk of hypoperfusion, sevoflurane is the alternative.[129]

3. Conclusions

In the literature reviewed, there is evidence to support the claim that both inhalational and intravenous anaesthetic agents may be useful instruments in ensuring the required degree of neuroprotection.[4,130]
and propofol, and most volatile and gaseous anaesthetics (halothane, isoflurane, sevoflurane, desflurane and xenon) show neuroprotective effects that protect cerebral tissue from adverse events – such as apoptosis, degeneration, inflammation and energy failure – caused by chronic neurodegenerative diseases, ischaemia, stroke or nervous system trauma. The length of this neuroprotection, under the right circumstances, is about 2–4 weeks and depends on the experimental model, control of physiological parameters and the assurance of the adequacy of reperfusion. In addition, anaesthetics (especially volatile anaesthetics) have been shown to accelerate post-ischaemic neurogenesis, suggesting that they may also enhance endogenous reparative processes in the injured brain.[131] Nevertheless, it is also true that several studies in the developing animal brain demonstrate that the administration of some volatile, gaseous and intravenous anaesthetics was associated with neurodegenerative effects.[12,13] Single drugs (especially halothane, isoflurane and ketamine), or a combination of them, seem to cause brain cell death and long-term neurocognitive dysfunction in neonatal rats in a dose-dependent and exposure time-dependent manner. Therefore, each drug exhibits advantages and disadvantages which, together with a patient's medical and surgical history, appear to be decisive in choosing the most suitable anaesthetic for the specific situation.[132] At present, available experimental data do not support the selection of any one anaesthetic agent over the others. Obviously, this is not surprising. In the absence of controlled studies, which demonstrate the superiority of one technique over another, we believe it is normal that interpretations of the available data differ, as well as opinions on the optimal approach.

Finally, given that many of the studies in the literature have been conducted in animals or *in vitro*, we believe that it is premature to change clinical practice because the issue has not been adequately studied in humans. Further investigations are imperative.

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