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Anesthetics and analgesics in experimental traumatic brain injury: Selection based on experimental objectives

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Abstract

The use of animal modeling in traumatic brain injury (TBI) research is justified by the lack of sufficiently comprehensive in vitro and computer modeling that incorporates all components of the neurovascular unit. Valid animal modeling of TBI requires accurate replication of both the mechanical forces and secondary injury conditions observed in human patients. Regulatory requirements for animal modeling emphasize the administration of appropriate anesthetics and analgesics unless withholding these drugs is scientifically justified. The objective of this review is to present scientific justification for standardizing the use of anesthetics and analgesics, within a study, when modeling TBI in order to preserve study validity. Evidence for the interference of anesthetics and analgesics in the natural course of brain injury calls for consistent consideration of pain management regimens when conducting TBI research. Anesthetics administered at the time of or shortly after induction of brain injury can alter cognitive, motor, and histological outcomes following TBI. A consistent anesthesia protocol based on experimental objectives within each individual study is imperative when conducting TBI studies to control for the confounding effects of anesthesia on outcome parameters. Experimental studies that replicate the clinical condition are essential to gain further understanding and evaluate possible treatments for TBI. However, with animal models of TBI it is essential that investigators assure a uniform drug delivery protocol that minimizes confounding variables, while minimizing pain and suffering.

Keywords

analgesics; anesthetics; pain; rodents; traumatic brain injury

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Additional Considerations

Differences in outcome among physically similar individuals following equivalent traumatic brain injuries can be particularly noticeable. Minimizing confounds of analgesic and anesthetic drugs are only one step toward conducting valid and reproducible animal modeling of TBI. Differences in weight, sex, age at injury, and genetic background can influence recovery by altering how individuals sustain the mechanical forces and endure the secondary injury processes of brain injury.

Introduction

Traumatic brain injury (TBI) is a serious health epidemic contributing to death and permanent disability. The United States Centers for Disease Control and Prevention estimate that 1.7 million individuals sustain a TBI annually in the United States alone¹. There is currently no pharmacological treatment for individuals who suffer the lifelong neurological morbidities associated with TBI and efforts to lower the high incidence are primarily preventive. Animal models have been designed to parallel pathological processes in humans to reproduce a consistent injury². The validity of TBI animal models to the clinical condition makes them powerful tools in evaluating post-traumatic morbidity and testing rational therapeutic interventions after brain injury. When using research animals, the consideration of animal welfare is vital and pain and distress should be minimized. However, the introduction of anesthetics during experimental TBI and the use of analgesics for post-traumatic pain management can interfere with post-injury processes and functional outcomes. In this overview, we discuss how the use of anesthetic and analgesic compounds can affect evaluation of functional and histopathological outcomes following experimental TBI and how their selection or exclusion should be established based on experimental objectives.

Need for TBI models

Federal research regulations require that all reasonable alternatives which could adequately answer the proposed question be explored before considering a study that incorporates animals. The complex neurovascular responses after TBI require investigations that involve the immune, circulatory, and central nervous systems of live animals. The long term consequences of diffuse TBI include a host of emotional, cognitive, and sensory deficits that can degrade quality of life. Specific aspects of brain injury, such as cell death, have been successfully modeled with *in vitro* neural injury^{3, 4}. However, *in vitro* models cannot be sustained over chronic time points to evaluate injury progression and lack the complex interactions among systems that characterize TBI neuropathy. Additionally, current computer models cannot reproduce the complicated pathophysiology of TBI. A wide range of well-accepted animal models are available for neurotrauma investigation (see table 1), and the use of whole animal models is justified for TBI research and deemed appropriate for conduct of pre-clinical studies⁵. Therefore, neurotrauma research necessitates live animal models of human TBI, which must be employed within the existing animal welfare regulatory environment.

Experimental Animal Models of TBI

Traumatic brain injury is a complex process characterized by two pathological phases: cellular injury resulting from a primary mechanical impact and the ensuing secondary injury mediated by pathological processes⁶. A range of experimental models of TBI are used in research differing in primary injury mechanisms. Biomechanical mechanisms of TBI can be classified as either focal or diffuse injury (see table 1). Each model can be used to answer specific scientific questions. The majority of experimental brain injury research relates to mild and moderate human injuries, which do not involve coma. For this reason, rodents are rarely kept in drug induced sedation or coma after injury. All brain injury models have been carried out beyond six months to evaluate histopathology, behavior, and biochemistry.

Animal Welfare in TBI Research

The privilege of conducting research on living animals demands high levels of responsibility. The use of animals in research must be justified from an ethical cost-benefit perspective where animal pain, morbidity, and mortality must be outweighed or balanced by

the potential benefits of the experimental findings to human or animal health, advancement of knowledge, or good of society. Investigators are obligated to minimize the amount of pain and distress in animals utilized for research. Withholding anesthetics, analgesics, or tranquilizers can only be allowed if it is scientifically justified by investigators and subsequently approved by an institutional animal care and use committee (IACUC). Studies in which animals are subjected to painful or stressful conditions without the use of anesthetics, analgesics, or tranquilizers are classified by the USDA and Animal Welfare Act as Category E. Category E studies must show that less painful or stressful alternatives are not available, or that less painful/stressful endpoints cannot be reasonably substituted. Since human TBI occurs in the absence of anesthetics and analgesics, which can confound outcomes (see below), scientifically well-justified, complete, and accurate studies using in vivo models of TBI can be classified as Category E procedures in which drugs can be withheld.

Pain and TBI

By its nature, TBI is associated with acute and chronic pain both in animal models and man^{27, 28}. The initial trauma elicits somatic pain and secondary injury mechanisms contribute to visceral and neuropathic pain²⁷. Measures to reduce nociception and distress should be implemented before, during, and following surgical procedures (deep, general anesthesia) and scientific objectives must be balanced against the use of anesthetics and analgesics in experimental animal models of TBI to protect animal welfare and prevent unnecessary suffering. Administration of anesthetics and analgesics can both positively and negatively influence post-injury processes and elicit functional changes in animal models of TBI, thus, these drugs should be selected based on experimental objectives. Consistent control of anesthetics and analgesics (drug choice and dose) throughout a study will help alleviate confounding factors that may influence post-injury outcome measures. The standardization of pain management within a study will also permit cross study comparisons. Pharmacological pain management immediately following experimental TBI in animal models can influence post-injury outcomes (see below), therefore selection should be based on IACUC approved experimental objectives. This review is intended to aggregate examples of research-based instances of anesthetic and analgesic interference on TBI outcome measures.

Anesthetics in TBI Research

Anesthetics induce a variety of reversible effects depending on the concentrations at which they are delivered²⁹. At lower concentrations inhaled anesthetics induce euphoria, amnesia, and hyperreflexia, but as concentrations increase anesthetics can lead to deep sedation and diminished somatic and autonomic responses to stimuli²⁹. Inhaled anesthetics target both the spinal cord and the brain with differing mechanisms of action. The amnesic actions of inhaled anesthetics are mediated within the brain, depressing blood flow and glucose metabolism, with greater levels of depression in regions such as the thalamus and midbrain reticular formation²⁹. Most inhaled anesthetics alter receptor-mediated synaptic signaling and consequently synaptic transmission³⁰. Absence of movement in response to painful stimuli can be mediated by anesthetic action on the spinal cord, whereas general anesthesia results from supraspinal sites of action^{29, 31, 32}. Local anesthetics are used for topical pain management by reversibly inhibiting sodium currents and thereby nerve impulses³³.

When using animal models to replicate clinical TBI, anesthetics are routinely administered during surgical procedures to minimize pain and discomfort as well as provide immobilization. However, anesthetics used during the induction of experimental TBI can interfere with histopathological and functional outcomes. Commonly used anesthetics can

provide varying degrees of neuroprotection, suggesting that the choice of anesthetics used in TBI models can greatly alter post-injury outcome³⁴. For example, isoflurane, an inhaled anesthetic commonly used in veterinary medicine, has been shown to facilitate functional outcome in comparison to other anesthetics following the controlled cortical impact (CCI) model of TBI in rats, possibly through modulation of excitotoxicity or an increase of cerebral blood flow³⁵. Rats anesthetized with isoflurane and subjected to CCI performed better on motor tests (beam balance, beam walking) as well as cognitive tests (Morris Water Maze) compared to rats anesthetized intravenously with fentanyl³⁵. Isoflurane also attenuated hippocampal damage, specifically to the CA1 region when compared to fentanyl³⁵. A follow-up comprehensive study evaluated cognitive outcome following CCI in the rat with the administration of several anesthetics and provided support that different anesthetics in experimental TBI critically influence outcome³⁶. In all cases, animals treated with anesthetics differed from untreated animals. Isoflurane-treated rats exhibited the most improved latency times in the Morris Water Maze compared to rats injected with fentanyl or diazepam, which trended toward longer latencies to locate the platform³⁶. The analysis of cresyl violet staining to investigate neuronal survival in brain tissue following CCI provided evidence that different anesthetics protect against cell death to varying extents. Again, isoflurane treatment demonstrated the most neuroprotection against hippocampal cell death, whereas rats treated with ketamine following CCI demonstrated the least protection against hippocampal cell death³⁶. Isoflurane modulates excitotoxicity by reducing the release of glutamate³⁷ as well as blocking NMDA receptors³⁸ which may mechanistically contribute to neuroprotection³⁶.

Although preconditioning with isoflurane has produced beneficial effects in animal models of TBI^{34–36, 39}, Hertle et al. recently published data suggesting deep sedation using isoflurane negatively influences neurological outcome in a rat model of TBI⁴⁰. Rats preconditioned with isoflurane and subjected to CCI demonstrated increased cortical damage assessed by apoptotic cell markers and a worsened neurological outcome measured by a standardized inclined plane test⁴⁰. Investigating the cerebral protective effects of anesthetics used in combination with hypothermia following diffuse TBI has shown that propofol may be a better treatment for head injury than isoflurane⁴¹. Propofol, a general injectable anesthetic similar to the inhalant isoflurane (both of which modulate GABA receptors^{41, 42}), used in combination with moderate hypothermia in rats subjected to diffuse impact-acceleration TBI significantly lowered intracranial pressure (ICP) and significantly raised cerebral perfusion pressure (CPP) compared to isoflurane combined with hypothermia⁴¹. Investigation of ICP and CPP after diffuse impact-acceleration brain injury in rats has shown that sevoflurane, a general inhalational anesthetic, raised ICP and caused a more pronounced decrease in CPP than observed with isoflurane treated animals⁴³. The authors proposed that different cerebrovasodilatory effects of each anesthetic can account for the effects in ICP⁴³. Similarly, administration of anesthetics themselves can affect physiological conditions which influence outcome. Anesthetic delivery can affect normal ventilation and carbon dioxide levels which consequently alter ICP, CPP, and cerebral blood flow (CBF)^{44–46}.

TBI initiates a cascade of secondary injury processes that define the disease. Studies including but not limited to the ones above have shown that administration of anesthetics shortly after experimental TBI can act on these secondary injury mechanisms to mitigate or possibly exacerbate damage. The administration of propofol in conjunction with the closed head injury model in rats alters the synthesis of nitric oxide, ultimately reducing lipid peroxidation⁴⁷. Yurdakoc et al. has shown similarly that, isoflurane given after closed head trauma may protect against lipid peroxidation⁴⁸. Altering lipid peroxidation, a secondary injury mechanism characteristic of TBI, provides evidence that specific anesthetics may

have neuroprotective effects on head injuries through pathophysiological pathways and may change the natural course of brain injury in animal models.

Anesthetic compounds which act as antagonists at the N-methyl-D-aspartate (NMDA) receptor may also exhibit neuroprotective properties^{49–51} that improve outcome from TBI⁵². Rats subjected to fluid percussion injury and administered ketamine, an injectable non-competitive NMDA receptor antagonist, showed preserved memory function⁵². However, intraperitoneal injections of ketamine given to rats before CCI did not prevent TBI induced intracerebral cytokine production and had minimal effect on the early local inflammatory response⁵³. Thus, ketamine can alter the course of brain injury through mechanisms other than inhibition of inflammation.

The administration of anesthetics during TBI modeling interferes with neurological outcome. Anesthetics can be neuroprotective, making them beneficial treatments for TBI, however, contradicting studies conclude that anesthetic administration may worsen outcome. For this reason, the use of anesthetics in TBI modeling should be standardized within studies to provide consistent timing and dosage. Compounds should be selected based on specific experimental objectives for each study in accordance with local and federal regulations. It is suggested that anesthetics be carefully controlled in studies exploring the natural course of brain injury to preserve validity.

Analgesics in TBI Research

Ethical standards have been developed and enforced to protect the well-being of animals used for biomedical research. This includes proper pain management following surgical procedures. However, post-surgical analgesics have been shown to be neuroprotective and may confound the evaluation of post-injury outcome measures^{54, 55}. Conversely, chronic administration of analgesics following TBI has led to worsened outcomes⁵⁶. Comprehensive dosing paradigms of common analgesic drugs have not been determined in all experimental TBI models. It is also not well known the degree of interference from drugs, whether subtle or substantial, on molecular, functional and behavioral outcomes. This inconsistency supports the claim that analgesics must be carefully considered and tested before being administered following TBI in order to maintain a valid and reproducible animal model.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly administered to mitigate inflammation and accompanying pain. During the inflammatory process, cyclooxygenase (COX) enzymes facilitate the conversion of arachidonic acid into inflammation-mediating prostaglandins^{57, 58}. NSAIDs act to reduce prostaglandin synthesis by inhibiting the production of COX-1 and COX-2⁵⁹. NSAIDs and specific COX-2 inhibitors are effective in suppressing inflammation, possibly by interfering with secondary injury mechanisms.

As an apparent contradiction to the acute neuroprotective actions of some NSAIDs, their chronic administration following TBI can negatively influence functional outcome⁵⁶. Ibuprofen administered chronically over a 4 month period to rats subjected to fluid percussion injury led to a worsening in cognitive function measured by the Morris Water Maze⁵⁶. These results show the complexity of analgesic administration post-injury and lend caution to the selection and duration of analgesics in animal models of TBI.

Carprofen, an NSAID, administered to mice after a closed head injury (CHI) results in improvements in neurobehavioral function⁶⁰. Mice receiving carprofen following TBI exhibited a more rapid and pronounced improvement of neurological deficits measured with the Neurological Severity Score when compared to mice receiving vehicle treatment⁶⁰. In addition, rats receiving nimesulide, a COX-2 inhibitor, after a diffuse TBI using the impact acceleration model showed improvement in functional and motor deficits⁶¹. Treatment with

nimesulide improved mean escape latencies over the post-injury assessment period in comparison to vehicle-treated controls using the Barnes circular maze to assess spatial reference memory. Motor deficits, measured using the rotarod test, were also attenuated after treatment with nimesulide following TBI⁶¹. Similarly, 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl-2(5H)-furanone (DFU), a selective COX-2 inhibitor, has been shown to improve neurological reflexes and memory when administered following cortical impact in the rat, as compared to administration of a vehicle control⁶². Thus, analgesics can interfere with the natural course of the injury toward an improved recovery of function.

Endogenous and administered opioids attenuate responses to many painful stimuli in both humans and animals. TBI causes increased release of endogenous opiate receptor agonists which contribute to the trauma-induced secondary injury cascade^{63–65}. For example, morphine administration immediately following TBI in the mouse confounds the evaluation of cognitive deficits as measured in the Morris Water Maze task⁶³, where mice treated with morphine immediately post-injury were protected from long-term but not short term cognitive deficits⁶³. Morphine has also been shown to reduce behavioral deficits when given to rats just prior to diffuse brain injury induced by fluid percussion^{66–68}. Morphine given in combination with scopolamine, a muscarinic receptor antagonist, provided even greater protection on motor performance⁶⁷. These results suggest that administering opioids following TBI alters the natural course of brain injury.

Further, the administration of analgesics following TBI not only alters functional outcome, but also alters the pathophysiological course of the injury. Brain-injured mice treated with carprofen had a significant decrease in lesion size post-injury⁶⁰. Carprofen-treated mice showed increased cell proliferation and gliogenesis in comparison to vehicle-treated controls⁶⁰. The administration of other analgesics, such as nimesulide, has been shown to alter cellular mechanisms following experimental TBI⁶¹. Rats subjected to an impact acceleration-induced TBI exhibited a marked increase in COX-2 protein expression in the hippocampus⁶¹. Based upon the hypothesis that COX-2 mediates the production of prostanoids (including prostaglandins), inhibiting COX-2 expression with an analgesic should attenuate aspects of secondary injury and neurological deficits following experimental TBI⁶¹. Administration of other analgesics following TBI in the rat attenuated the amount and intensity of immunoreactive COX-2 in the cortex as compared to vehicle-treated controls⁶². Rats administered analgesics after TBI have also shown a decreased number of activated caspase-3-immunoreactive cells in both the injured cortex and hippocampus⁶². Thus, the administration of analgesics post-injury can prevent cell death and alter the pathophysiology of experimental TBI. For these reasons, it is imperative to design analgesic protocols for post-operative care that do not inhibit the processes being evaluated following experimental TBI.

While analgesics and anesthetics have great potential to confound the natural course of brain injury, justified pain management in experimental animals remains of utmost concern. Investigators have the obligation to minimize animal pain and distress in their research protocols. Perioperative pain management should be based on experimental objectives in light of the potential confounds on assessment outcomes.

Conclusions

Valid animal modeling of TBI requires accurate replication of both the mechanical forces and secondary injury conditions experienced by human patients. The interference of anesthetics and analgesics in the natural course of brain injury calls for special consideration of pain management drugs when conducting TBI research. Our analysis of these studies

indicates that anesthetics administered at the time of or shortly after the impact alter outcome following TBI. To protect animal welfare anesthetics cannot be completely avoided, however, a consistent (drug and dose) intra-study anesthesia protocol is imperative when conducting TBI studies. Similarly, studies indicate the administration of analgesics to control perioperative pain may alter outcome following TBI. Due to the variability among traumatic brain injury models and experimental outcome measures, uniform recommendations for anesthesia and analgesia are not practical. For this reason, recommendations for specific drug choice and dosing were not included in this review. Investigators are urged to establish a standard of animal care specific to individual experimental objectives based on pilot study data.

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Table 1

Summary table of representative animal models of traumatic brain injury including mechanism of injury and degree of surgical invasiveness.

Traumatic Brain Injury Models		
Model	Description	Refs
Fluid Percussion Injury (FPI)	Fluid pressure pulse delivers mechanical forces onto exposed brain. Can be performed laterally or centrally. Requires craniectomy.	7–10
Controlled Cortical Impact (CCI)	Computer controlled pneumatic piston drives into cortex, creating a focal injury. Requires craniectomy.	11–13
Blast Injury	Compressed gas delivers pressure wave, resulting in a diffuse injury. Minimal surgical preparation.	14–16
Impact Acceleration Injury	Weight is dropped onto head supported by foam pad. Scalp incision may be required.	17–19
Weight Drop Injury	Weight is dropped onto head supported by metal base. Scalp incision may be required.	20–23
Penetrating Injury	Projectile is driven into the brain causing a focal injury. Requires craniectomy.	24–26

Summary table of anesthetic and analgesic effects on the natural course of behavioral, histological, and physiological outcomes from experimental brain injury. Experimental objectives assessed using (+) to indicate improvement or positive outcome and (–) to indicate worsening or negative outcome. CCI=Controlled Cortical Impact, WD=Weight Drop, IA=Impact Acceleration, FPI=Fluid Percussion Injury.

Table 2

Anesthetic & Analgesic Effects					Refs
Drug	TBI Model	Behavioral	Histological	Physiological	
Isoflurane	CCI	+	+		34, 35
Isoflurane	CCI			+	36–38
Isoflurane	CCI	–	–		40
Isoflurane	WD			+	48
Propofol	IA			+	41
Sevoflurane	IA			–	43
Propofol	WD			+	69
Ketamine	FPI	+			52
Ketamine	CCI	+	+	–	70
Carprofen	WD	+	+		60
Nimesulide	IA	+		+	61
DFU	CCI	+		+	62
Morphine	WD	+			71
Morphine	FPI	+			67
Scopolamine	FPI	+			67
Ibuprofen	FPI	–			56