Anesthesiology
70:967–972, 1989

Halothane, Fentanyl/Nitrous Oxide, and Spinal Lidocaine Protect Against Spinal Cord Injury in the Rat

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Little information is available regarding the interaction of anesthesia and spinal cord injury. In this study male, Sprague-Dawley rats (n = 140) of similar weights underwent a graded lumbar spinal cord injury by inflation of an epidural balloon, to determine the effect of anesthesia upon the severity of injury. One of three different anesthetic regimens (halothane, fentanyl/nitrous oxide, or spinal lidocaine) were administered during the time of injury, and the neurologic outcome was compared to an awake control group. Physiologic variables (*p*H, Pa_{CO_2}, Pa_{O_2}, hematocrit, mean arterial pressure, serum glucose, and temperature) were maintained within normal ranges. Dose-response curves were constructed evaluating the relationship between the duration of balloon inflation *versus* the percentage of animals with a sustained neurologic deficit. The dose-response curves were analyzed for differences by use of a group *t* test. The incidence of clinical spinal cord injury (hindlimb paralysis) was lower in all three anesthetic groups as compared to awake controls ($P < 0.05$). The balloon inflation time required to produce a sustained neurologic deficit in 50% of rats for each group was (minutes [mean ± SD]): 1) awake—10.0 ± 2.3; 2) spinal lidocaine-19.6 ± 11.6, 3) halothane—19.8 ± 6.7; and 4) fentanyl/nitrous oxide—37.9 ± 18.7. This observation demonstrates that, in this model of spinal cord injury, various anesthetics improve neurologic function as compared to the awake state. It does not indicate any one technique as being either more favorable or deleterious in determining the final neurologic outcome. The precise mechanism(s) explaining how anesthetics decrease the incidence of spinal cord injury are likely to be multiple, complex, and as yet not totally understood. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, local: lidocaine. Anesthetics, opioids: fentanyl. Anesthetics, volatile: halothane. Spinal cord: injury.)

PATIENTS FREQUENTLY require anesthetic management in clinical situations where there is a risk of spinal cord injury. Neurologic deterioration may occur either as a result of a direct primary insult, or subsequent extension of the primary injury due to secondary pathophysiological factors. Various drugs and modalities have been demonstrated to favorably affect neurologic outcome in association with spinal cord injury.

Treatment regimens that have a beneficial effect on outcome may simplistically be grouped into two categories. The first category includes factors that decrease the metabolic requirements of the spinal cord, thus transiently increasing the tolerance to primary injury. Metabolic depression is accomplished either by decreasing the internal energy requirements and/or the synaptic activity of the neuron. Treatment regimens that decrease metabolism and have demonstrated favorable effects upon spinal cord injury include hypothermia, barbiturates, magnesium, and lidocaine.[1–7] Many anesthetics are known to decrease cerebral and spinal cord metabolism.[8] Accordingly, anesthetics may produce a favorable effect upon the extent of spinal cord injury.

A second treatment category includes modalities that positively modify secondary pathophysiological factors, and favorably affect neurologic outcome following spinal cord injury.[9–16] One group of drugs that has produced beneficial effects on spinal cord injury are opiate antagonists, of which naloxone has been extensively studied.[11–19] It has been proposed that endogenous opioids may mediate secondary injury *via* the kappa receptor, which is upregulated following spinal cord injury.[19] The theory developed by Faden is that endogenous opioids act at spinal cord kappa receptors and cause a decrease in spinal cord blood flow, which results in a worse neurologic outcome.[12,15,16,19] One kappa agonist (dynorphin) has been observed to directly produce hindlimb paralysis.[17] In addition, opiate antagonists have been observed to increase spinal cord blood flow following injury, and improve neurologic outcome;[11,12,15,16,18] thus providing direct evidence and a physiologic explanation for opioid involvement in the pathophysiology of spinal cord injury. If narcotic antagonists result in a favorable effect on spinal cord injury with at least one endogenous opioid producing a detrimental effect, by inference, does a narcotic-based anesthetic have a detrimental effect upon neurologic outcome following spinal cord injury?

In the present study, three different anesthetics (halothane, fentanyl/nitrous oxide [N_2O], and spinal lidocaine)

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Received from the Departments of Anesthesiology and Neurology, Veteran's Administration Medical Center, San Diego, California; University of California at San Diego, La Jolla, California; and the Department of Anesthesiology, Loma Linda University, Loma Linda, California. Accepted for publication January 5, 1989.

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were evaluated in order to determine a potential interaction between anesthesia and spinal cord injury.

Materials and Methods

Following approval by the Institutional Animal Studies Subcommittee, male, Sprague-Dawley rats (n = 140) of similar weights were randomly separated into three anesthetic groups, and an awake control group. The surgical preparation consisted of the following.

Day 1

N_2O/isoflurane anesthesia was delivered *via* a face mask. A subarachnoid catheter (PE-10) was inserted *via* the atlanto-occipital membrane according to Yaksh and Rudy,[20] with the tip positioned at T_8 (verified at necropsy). The catheter was sutured in place, and the incision was closed and infiltrated with 0.25% bupivicaine. A 24-h anesthetic recovery period was allowed, during which periodic neurologic evaluations were performed. The neurologic exam consisted of: 1) observation of the rat for state of alertness, grooming, and response to cage movement, 2) observation of the functional use of all four extremities and the gait during ambulation, 3) motor response of all four extremities, and 4) response to sensory stimuli.

Day 2

Normal neurologic function was verified, and each rat was reanesthetized with N_2O/isoflurane *via* a face mask. A catheter (PE-50) was inserted into a tail artery and secured in position. A midline lumbar laminectomy was performed at L_{3-4}. A balloon tipped 2-French Fogarty® catheter was advanced 1.5 cm into the lumbar epidural space with the tip located at the thoracolumbar junction. The catheter was sutured in place, and the incision was closed and both incisions were infiltrated with 0.25% bupivicaine. The surgical period lasted approximately 45 min, after which each rat was allowed a 120-min anesthetic recovery period. Normal neurologic function was verified, and each rat was randomized into one of the following groups.

Control (n = 38). Animals were awake and unrestrained during the spinal cord injury. Thirty μl of preservative free saline was administered *via* the subarachnoid catheter at the time of spinal cord injury.

Treatment 1 (n = 34). Fentanyl 57 μg/kg (subcutaneously) and 65% N_2O was administered during the spinal cord injury. Thirty μl of preservative-free saline was given *via* the subarachnoid catheter at the time of spinal cord injury.

Treatment 2 (n = 34). End-tidal halothane, 1.33–1.44% (measured by a Perkin-Elmer mass spectrometer), was administered during the spinal cord injury. Thirty μl of preservative-free saline was given *via* the subarachnoid catheter at the time of spinal cord injury.

Treatment 3 (n = 34). Thirty μl of 5% lidocaine was administered *via* the subarachnoid catheter prior to the spinal cord injury in order to maintain a block above the thoracolumbar junction for >35 min.

Each anesthetic dose was determined based upon previous studies, in an attempt to provide an anesthetic level roughly equivalent to 1.3 MAC.[21,22] Lidocaine group rats had a lidocaine analgesia regression evaluation performed the previous day in order to provide a predictable block at or above the thoracolumbar junction throughout the insult period. The analgesia regression evaluation consisted of verifying that the lidocaine dose (30 μl) blocked all stimulation below T_{12} for at least 35 min. Stimulation consisted of lower extremity movement (proprioceptive response) and pinch of the paw and skin (noxious stimuli). The level of lidocaine blockade was evaluated every 3 min.

Physiologic parameters (*p*H, Pa_{CO_2}, Pa_{O_2}, mean arterial pressure [MAP], serum glucose, and hematocrit) were monitored immediately prior to and during the spinal cord injury. Rectal temperature was servo-controlled at 37° C with a heat lamp. The awake group and the lidocaine group were allowed to spontaneously ventilate in an oxygen enriched atmosphere (FI_{O_2} = 40%) during the spinal cord injury. The fentanyl/N_2O and halothane group were orotracheally intubated (under the study anesthetic) prior to the spinal cord injury, and mechanical ventilation was adjusted to maintain physiologic arterial blood gases.

When anesthetic equilibrium was attained, the epidural balloon was inflated with a constant volume of air (0.1 ml) over varying times (0, 3, 6, 9, 20, or 35 min) that were chosen to produce all degrees of spinal cord damage. After spinal cord insult, the epidural and arterial catheters were quickly (<10 min) removed under N_2O/isoflurane anesthesia. Each rat was awake, and spontaneously ventilating within 5 min following catheter removal. Following anesthetic recovery, each rat was neurologically evaluated by an investigator blinded to treatment through 7 post-insult days. The neurologic evaluation was performed at a similar time each day, and established the presence or absence of hindlimb paralysis. Hindlimb paralysis was defined as the absence of spontaneous and purposeful (response to noxious stimulus) movement of either hindlimb. A flicker of movement did not qualify as purposeful movement. A rat that had a purposeful response to noxious stimuli but exhibited no spontaneous movement of the graded extremity was not graded as paralyzed.

During the post-insult days, meticulous nursing care was administered to each rat consisting of the following: 1) one cage was allotted to each rat; 2) all rats were kept in a heated environment; 3) bladders were voided twice

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TABLE 1. Measured Physiological Data (Mean ± SD)

	A (n = 38)	L (n = 34)	F/N (n = 34)	H (n = 34)
Weight (grams)	315 ± 19	306 ± 16	310 ± 16	311 ± 16
MAP (mmHg)	110 ± 13*	100 ± 9*	108 ± 9	91 ± 10*
Pa_{CO_2} (mmHg)	40.7 ± 2.9	39.2 ± 4.0	39.2 ± 3.0	39.2 ± 3.3
Pa_{O_2} (mmHg)	111.4 ± 32.2	110.5 ± 42.4	109.8 ± 18.8	97.1 ± 20.6
*p*H (units)	7.41 ± 0.04	7.42 ± 0.04	7.42 ± 0.03	7.42 ± 0.04
Hematocrit (%)	42 ± 2	41 ± 4	42 ± 2	40 ± 3
Glucose (mg/dl)	150 ± 11†	164 ± 36	209 ± 47†	163 ± 28

A = awake group; L = spinal lidocaine group; F/N = fentanyl/nitrous oxide group; H = halothane group.

* Statistically significant difference between the awake group and the lidocaine and halothane group ($P < 0.05$).

† Statistically significant difference between the awake group and the fentanyl/nitrous oxide group ($P < 0.05$).

daily using a Credé maneuver; 4) intramuscular gentamicin (1 $mg \cdot kg^{-1}$) was administered each day; 5) each rat was bathed daily; 6) each rat was weighed daily and subcutaneous fluids were administered dependent upon the presence and magnitude of any weight loss; and 7) each rat had al lib access to Tekland rodent chow.

HISTOPATHOLOGY

A qualitative histopathologic analysis of the injury to the spinal cord was achieved as follows. Different male, Sprague-Dawley rats (n = 3) with similar weights (300–350 g) received a spinal cord injury *via* balloon inflation (ED_{95}) during halothane anesthesia. The rats were recovered in a similar manner as above through 7 post-insult days. On the eighth post-insult day, each rat was anesthetized with halothane and perfused *via* the left ventricle with 10% buffered formalin for 20 min. The spinal cords were excised and placed in 10% buffered formalin solution. The cords were then sectioned in standard fashion for H & E staining, at the site of injury and directly above and below the injury. The spinal cord was qualitatively analyzed by a neuropathologist blinded to the experimental protocol.

Statistical analysis was performed on the physiologic data using Dunnett's *t* test comparing treatment groups to control.[23] Evaluation of the relationship between the duration of balloon inflation and the fraction of animals graded with a neurologic deficit (hindlimb paralysis) was done by constructing dose-response curves according to Zivin *et al.*[24] The equation of the logistic function is: $P = D^s/(D^s + M^s)$. P is the probability of a deficit, D is the duration of occlusion, M is the mean time required to produce deficits, and s is the slope of the logistic curve. This method is analagous to the pharmacologic evaluation of a drug effect described by Waud.[25] With this method, incremental differences in the dose of a drug are administered and an effect measured. A dose of a drug can be determined that produces the effect in 50% of the subjects (effective dose [ED_{50}]), or any other fraction. The ED_{50} dose-response concept is familiar, and has been converted to central nervous system injury in terms of an effective time (ET).[24] This method provides a way of quantitating central nervous system dysfunction, and affords a statistical tool to evaluate the efficacy of spinal cord treatment regimens. A curve was constructed on post-insult days 1 and 7. The two curves within an anesthetic group (day 1 and day 7) were compared for evidence of recovery (*i.e.*, if the curve on day 7 was significantly shifted to the right with respect to the curve from the same animals on day 1, the findings would be interpreted as demonstrating recovery). In addition, the curves were compared at day 7 for differences in outcome between control and treatment groups. The curves were analyzed for slope and effective time differences by use of a group *t* test. A *P* value of less than 0.05 was considered significant.

Results

The physiologic data (immediately prior to and during the spinal cord injury) are presented in table 1. There were differences in the MAP between the awake group (110 ± 13 mmHg) and the lidocaine (100 ± 9 mmHg) and halothane (91 ± 10 mmHg) groups. Differences were also observed in the serum glucose concentration between the awake group (150 ± 11 $mg \cdot dl^{-1}$) and the fentanyl/N_2O group (209 ± 47 $mg \cdot dl^{-1}$).

Recovery was evident in an occasional rat over the 7-day post-insult period; however, there was no statistical evidence of recovery when the study groups were evaluated as a whole. The dose-response curves for post-insult day 7 are presented in figure 1, and summarized in table 2 as ET_{50}s. The duration of balloon inflation is plotted against the percentage of animals with a clinical deficit in figure 1. There were significant differences in the dose-response curves in all anesthetized groups as compared to the awake group. These observed differences demonstrate a relative decrease in the incidence of spinal cord injury when an anesthetic was administered, as compared to the awake state.

Seventeen rats were excluded from the study. Seven were excluded because of a neurologic deficit following

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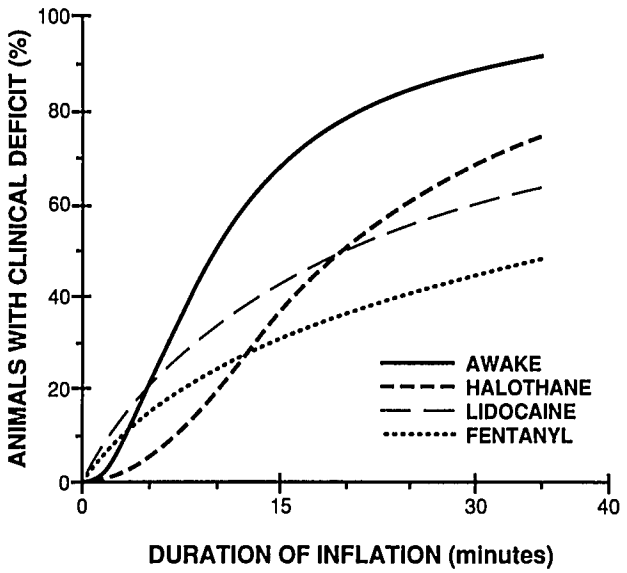

FIG. 1. Post-insult day 7 dose-response curve demonstrating the percentage of animals with a clinical neurologic deficit (paraplegia) as a function of the balloon inflation time in the lumbar epidural space. All three anesthetic regimens (n = 34 in each group) demonstrate a significant decrease in the incidence of sustained neurologic deficits as compared to the awake control group (n = 38), $P < 0.05$.

placement of the subarachnoid catheter. Two were excluded because of a neurologic deficit following placement of the epidural catheter. Eight rats died in the post-insult period. The deaths were equally distributed between all groups, and with one exception the deaths occurred in paralyzed animals. Thus, post-insult deaths should not have affected the interpretation of the study. When a rat was discarded, all data from that animal was removed from final analysis and that portion of the study was repeated in its entirety.

Histopathologic analysis revealed substantial injury at L_{1-2}. There was no histologic injury to the nerve roots or the cauda equina. The injury to the spinal cord involved the posterior columns and central grey matter and included 40–50% of the spinal cord cross-sectional area. The longitudinal progression of the injury was limited with a relatively rapid transformation from injured to normal cord. The injury was characterized by a total disorganization of the normal cytoarchitecture and a very heavy infiltration of macrophages and polymorphonuclear leukocytes. There were notable areas of hemorrhagic infiltrate and/or cellular debris.

TABLE 2. Time of Epidural Balloon Inflation Required to Produce a Neurological Deficit in 50% of Animals (ET_{50} [Mean ± SD])

Group	ET_{50} (Min)
Awake (n = 38)	10.0 ± 2.3
Lidocaine (n = 34)	19.6 ± 11.6*
Halothane (n = 34)	19.8 ± 6.7*
Fentanyl/nitrous oxide (n = 34)	37.9 ± 18.7*

* Indicates a significant difference between the awake group and the three anesthetic groups ($P < 0.05$).

Discussion

The observed decrease in the incidence of spinal cord injury by halothane, fentanyl/N_2O, and spinal lidocaine may have been due to multiple causes. One possibility that should be addressed includes physiologic factors, which may have had an effect on the final position of a particular dose-response curve. The scope of this study was to administer an anesthetic regimen in a clinically analagous manner. As a result, all physiologic variables inherent to a particular anesthetic regimen were allowed to contribute to the final neurologic outcome. Accordingly, we made no attempt to tightly control the physiologic state beyond maintaining it within clinical ranges. Of additional note, when differences were present, the physiologic data from the awake group was theoretically the most favorable in terms of limiting the extent of the spinal cord injury (highest MAP, lowest serum glucose [see table 1]).[26,27] Consequently, if the physiologic parameters of the anesthetic treatment groups had been similar to the awake control group, even greater anesthetic protection may have been demonstrated. Thus, while physiologic factors may have had a role in the final position of an individual dose-response curve, the observation that anesthetics decrease the incidence of clinical spinal cord injury in this model is still valid.

One methodological obstacle involved the removal of the arterial and epidural catheters. As this procedure involved noxious stimuli, anesthesia was required (for the two conscious animal groups). Accordingly, a standardized anesthetic regimen (60% N_2O and 1% isoflurane) was administered to all study groups during catheter removal. Alternatives included removal of the catheters while the animal was awake, which was not ethically acceptable; or to remove them later in the course of recovery. We did not feel it was acceptable to leave a foreign body in proximity to the injury. As a result, it was felt that quick (<10 min) removal of the catheters, with low doses of anesthesia, would provide a technique that was both ethically acceptable and had a minimal effect upon outcome.

One difficulty in performing comparative anesthetic studies is in attaining "equal" levels of anesthesia. As each anesthetic technique was qualitatively unique, it is likely that qualitative anesthetic differences were present in the central nervous system. However, comparative anesthetic studies provide useful information, and inherent differences that may occur should be further evaluated and not disregarded. Although the anesthetic levels cannot strictly be equated, an attempt was made to minimize this prob-

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lem, and anesthetic equivalents of 1.3 MAC were administered.[21,22] An additional question regarding the anesthetic groups is the fentanyl/N_2O combination. For this group, one cannot be sure whether a similar effect on spinal cord injury would have been observed had only N_2O or only fentanyl been administered. The choice of a fentanyl/N_2O anesthetic was decided on in order to determine the effect of this anesthetic regimen upon spinal cord injury, and not to evaluate a specific drug.

The most likely major mechanism of injury in this model is ischemia, with only a relatively minor degree of mechanical trauma in effect.[28] This speculation is based on the fact that the histopathologic injury was confined to the posterior spinal circulation. Additionally, in pilot studies when the epidural balloon was inflated to maximal capacity (0.2 ml) for 60 s, 100% of the animals were permanently paralyzed. This immediate and permanent paralysis should be due to mechanical forces. Conversely, ischemic pathology should require a longer insult time, as the injury is a result of sustained metabolic processes and not immediate mechanical forces. The fact that the present model produced a relatively high ED_{50} (table 2) in comparison to the insult time frame in the pilot studies would favor ischemia as a major contributor to the injury process.

The observation that three unique anesthetic regimens provide a similar reduction in the incidence of spinal cord injury suggests multiple mechanisms of injury/recovery as explanations. Possible mechanisms that may interact with anesthesia include: 1) metabolism, 2) blood flow, 3) catecholamine interactions, 4) opiate receptor activity, and 5) variations in prostaglandins, neurotransmitters, and other physiologic factors.[29] Based on observations in the central nervous system, it is likely that the subarachnoid lidocaine and halothane provided the greatest degree of metabolic suppression,[8,30–38] thus possibly allowing the neuron to tolerate longer periods of ischemia.

The MAP differences would suggest that the fentanyl/N_2O and awake groups had the most favorable spinal cord perfusion pressure. Increased catecholamine levels may have had a deleterious effect upon the extent of spinal cord injury.[39,40] Although serum catecholamine levels were not determined, it is likely that the fentanyl/N_2O anesthetic group had the greatest concentration (based on serum glucose as an indicator of stress[40]). In comparing three anesthetic groups to an awake control group, a prediction may have been made that the awake group would have been the most stressed, with a consequent higher catecholamine level. However, it should be remembered that, prior to the spinal cord injury, each animal spent 120 min in an undisturbed environment. In the awake animals, all that was necessary to produce the spinal cord injury was to inflate the epidural balloon from a distance of 60 cm (the length of the catheter) without otherwise disturbing the animal. Neglible differences in serum glucose were evident between the awake group and the lidocaine and halothane groups. However, the fentanyl/N_2O group demonstrated a significant increase in the serum glucose as compared to the awake control group. As N_2O results in sympathetic stimulation and increases in the catecholamine levels,[41] it is plausible that the awake group was minimally stressed with low catecholamine levels, and the anesthetic groups were also minimally stressed (with the increase in serum glucose observed in the fentanyl/N_2O group attributable to the inclusion of N_2O in the anesthetic regimen). If catecholamines were the only variable determining the extent of spinal cord injury, one would have expected the fentanyl/N_2O group to have demonstrated the greatest incidence of spinal cord injury, rather than the least. However, it is possible that anesthesia may result in a nonspecific reduction in stress that was not detected by serum glucose.

It is obvious that the fentanyl/N_2O anesthetic regimen should have profoundly interacted with spinal cord opiate receptors. If one subscribes to the hypothesis that opiate receptor agonists decrease spinal cord blood flow with a consequent adverse effect upon neurologic outcome,[16] the fentanyl/N_2O group would have been predicted to demonstrate the worst dose-response curve. In fact, the fentanyl/N_2O dose-response curve was no worse than the other two anesthetic techniques. Does this contradict the previous observations of opiate agonists causing a decreased spinal cord blood flow, hence a worse neurologic outcome? We feel not; rather, it assimilates into an overall complex explanation of spinal cord injury/recovery and anesthetic interaction. Most likely there is not a simple explanation of the pathophysiology of spinal cord injury, and multiple mechanisms of spinal cord injury/recovery are probably simultaneously in effect. An additional question must also be asked: Is the reduced spinal cord blood flow that is observed with opiates and spinal cord injury a direct result of opiates, or do opiates exacerbate spinal cord injury by other mechanisms, and are only circumstantially associated with the decrease in spinal cord blood flow? Other neurophysiological variables, prostaglandin interactions, and neurotransmitter interactions may have also had a role in the outcome in an as yet undetermined way.

In summary, three unique anesthetic regimens were found to decrease the incidence of spinal cord injury in the rat, as compared with that in an awake control group. This study indicates that the anesthetic state reduces the incidence of spinal cord injury, with no technique (of the ones studied) being indicated or contraindicated. The present study would also tend to exonerate opioid anesthetics from a detrimental effect on spinal cord injury, and provides no data to justify restriction of their use in today's anesthetic practice. The precise mechanisms

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whereby protection was afforded may be multiple and complex. Further laboratory studies are indicated to elucidate whether the observed beneficial effects of anesthesia are due to physiologic variables, anesthetic properties, a combination of both, or as yet unknown factors.

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