BASIC INVESTIGATIONS

Effects of Cocaine in an Experimental Model of Traumatic Brain Injury

Brian D. McBeth, MD, Susan A. Stern, MD, Xu Wang, MD,
Michelle Mertz, MS, Brian J. Zink, MD

Abstract

Background: Cocaine intoxication is found in a significant subset of emergency department (ED) patients presenting with traumatic brain injury (TBI). **Objectives:** To investigate the effects of acute cocaine intoxication on physiologic and metabolic parameters in a model of experimental TBI. **Methods:** Under inhalational anesthesia, swine were instrumented and subjected to fluid percussion TBI of 3 atm. Two groups were studied: TBI and cocaine ($n = 7$) and TBI only ($n = 7$). Two sequential doses of cocaine hydrochloride were administered intravenously to the animals receiving cocaine: 4 mg/kg 10 minutes prior to injury and 2 mg/kg 1 minute prior to injury. Control animals received normal saline. Cardiorespiratory and cerebral physiologic data were monitored for 180 minutes following injury. Cerebral blood flow (CBF) was measured using dye-labeled microspheres. Serum cocaine levels were measured by gas chromatography/mass spectrometry. **Results:** Mean (±SD) cocaine levels at the time of injury were 1,771 (±403) ng/mL. All animals survived the 180-minute observation period. There was a trend toward higher intracranial pressure (ICP) in the control (15.4 ± 8.2) vs. cocaine-treated (11.1 ± 5.8) animals, although this did not reach statistical significance (p = 0.18). Cerebral venous lactate (CVL) levels also trended higher in the control (1.14 ± 0.22) vs. cocaine-treated (0.91 ± 0.19) groups (p = 0.06). Cerebral perfusion pressures (CPPs), however, did not differ between groups. The CBF values decreased significantly from baseline in both groups but were not different between groups. **Conclusions:** Cocaine-intoxicated animals subjected to TBI showed no significant difference in primary outcome measures of CPP or CBF, although a nonsignificant trend toward lower ICP was noted. Overall, acute cocaine intoxication did not adversely affect the physiologic parameters examined in this TBI model. **Key words:** traumatic brain injury; cocaine. ACADEMIC EMERGENCY MEDICINE 2005; 12:483–490.

Traumatic brain injury (TBI) is a significant societal problem, with considerable morbidity, mortality, and monetary costs. The Centers for Disease Control and Prevention estimate that annually, almost 1.3 million people sustain a TBI, with 280,000 hospitalizations and 50,000 deaths.[1–4] Most patients who sustain significant injuries present to emergency departments (EDs) for initial stabilization and treatment.

There is clearly an association between trauma and cocaine abuse/intoxication, as noted in multiple clinical studies.[5–7] There is also a significant subset of patients who present to EDs with TBI and concurrent cocaine intoxication, although these statistics are not as well documented. As of 1997, estimates from urban centers suggest that there are 1.5 million cocaine users

in the United States.[8] In 1996, it was estimated that there were more than 150,000 annual ED presentations related to cocaine intoxication and cocaine-related incidents, representing a 78% increase from 1990.[8]

Cocaine has direct effects on the cerebral blood vessels and neurologic physiology. It is a sympathomimetic, and blocks norepinephrine, dopamine, and serotonin reuptake. This results in elevated levels of these neurotransmitters at the synapse level.[9] At higher doses, it can cause vasospasm, platelet aggregation, and acute thrombosis, which can result in myocardial infarction or stroke.[9,10] Tachycardia and hypertension from sympathomimetic stimulation are common. Cocaine-induced cardiac dysrhythmias are common as well, and may result from increased myocardial oxygen demand, acute vasospasm, or sodium channel blockade.[9,11] In TBI, cocaine could either increase cardiac output secondary to its sympathomimetic effects or compromise cardiac output in the setting of ventricular arrhythmias or acute vasospasm, with resulting effects on cerebral blood flow (CBF). In addition, acute cerebral vasospasm might primarily decrease CBF, again increasing the potential for secondary brain injury following the primary event, although, to the best of our knowledge, these effects have not been demonstrated in an animal model. With a greater understanding of the physiologic effects of cocaine in

this setting, one might be able to better monitoring and resuscitation of cocaine-intoxicated TBI patients in the ED. For example, if it were known that cerebral perfusion pressure (CPP) and CBF were lower in these patients, theoretically resuscitating to higher mean arterial pressures (MAPs) may be appropriate. Knowledge of cocaine's effects could affect choice of anesthesia and other pharmacotherapy, for similar reasons. Also, earlier invasive intracranial monitoring could be considered in cocaine-intoxicated patients if deleterious effects were demonstrated.

Other sympathomimetic agents have been shown to improve neurologic recovery in brain-injured animals. D-amphetamine accelerates recovery of motor function and visual deficits in rats and cats subjected to cortical ablation.[12–15] This may be in part due to increased levels of circulating catecholamines.[16] Very few studies have assessed the effects of acute cocaine intoxication on TBI. Muir et al., using a model of fluid percussion TBI in rats, demonstrated that animals pretreated with cocaine experienced lower blood pressures following injury, although CBF was actually higher at one hour post-injury.[17,18] The cocaine-intoxicated animals had milder motor deficits following injury, but there was no difference in cognitive function. We know of no published investigations using large animal models that have studied the effect of cocaine in TBI on physiologic and cerebrovascular parameters.

Our study sought to investigate the effects of acute cocaine intoxication in a large animal model of TBI that would better replicate human physiology. The hypothesis was that animals subjected to acute cocaine intoxication would have lower CPPs, poorer CBFs, and a decreased cerebral oxygen extraction ratio (CO$_2$ER) compared with control animals. It was believed that the sympathomimetic effects of hypertension and increased vascular resistance as well as acute cerebral vasospasm would predominate and compromise these primary outcomes. The aim was to delineate the acute effects of the drug on these and other important physiologic and metabolic parameters in the setting of a significant TBI.

METHODS

Study Design. This was a laboratory investigation of the effects of cocaine on animals subjected to TBI. Swine were chosen for this investigation because their physiologic response to intoxication and TBI simulates the human physiologic response more closely than any other nonprimate model. Immature swine have cardiovascular, cerebrovascular, hematologic, and electrolyte profiles that are almost identical to those of young humans.[19–26] A fluid percussion injury model was chosen because it has been studied extensively, is highly reproducible, and incorporates secondary injury.[27–35] Ventilation was controlled and

oxygenation maintained, because this closely simulates the clinical picture, following management guidelines for TBI that include early intubation and controlled ventilation.[9] The protocol was reviewed and approved by the University Committee on Use and Care of Animals at the University of Michigan, and was in accordance with the National Institute of Health guidelines for ethical animal research.

Animal Subjects and Preparation. Immature, mixed-breed swine of either gender, weighing 18–23 kg, were fasted the night prior to the experiment but allowed free access to water. Animals were initially sedated with ketamine (20 mg/kg intramuscularly), followed by a combination of halothane (2%), nitrous oxide (65%), and oxygen (33%) via nose cone. Once a surgical plane of anesthesia was reached, the animals were intubated and the halothane concentration was reduced to 0.75%.

The right femoral artery and vein were isolated by direct cutdown, and cannulated for blood sampling and blood pressure monitoring. The right external jugular vein was cannulated and a pulmonary artery (PA) thermodilution catheter was inserted and advanced into the PA for monitoring of central venous pressure (CVP), PA pressure, cardiac output, core body temperature, and mixed-venous blood sampling. A pigtail catheter was inserted via the right external carotid artery into the left ventricle for colored microsphere injection for measurement of CBF and renal blood flow (RBF).

The animal was then placed prone on the table in a head stabilizer, and a 16-mm diameter craniotomy was created immediately anterior and to the right of the bregma. A T-shaped bolt was screwed into the craniotomy site so it abutted the intact dura. This bolt was connected to the fluid percussion device, and to a high-pressure transducer, which permitted quantification of the force delivered. A second craniotomy was performed in the left posterior parietal region for placement of a neonatal intraventricular catheter in the left lateral ventricle for intracranial pressure (ICP) monitoring. A third craniotomy was created in the left anterior skull, 10–12 mm anterior to the ICP site. The dura was coagulated and a Licox MCB Oxygen Monitor probe (Integra Life Sciences, Plainsboro, NJ) was inserted obliquely through the cerebral cortex to rest in the gray matter of the left parietal cortex. A Licox temperature probe was also inserted through the second craniotomy site. Through a fourth craniotomy just anterior to the inion, a 20-gauge catheter was placed in the sagittal sinus for cerebral venous blood sampling. All craniotomy sites were sealed with dental cement (Figure 1).

Study Protocol. Cocaine was administered via the intravenous (IV) route, because this yields the most reproducible results and is the route of choice in the
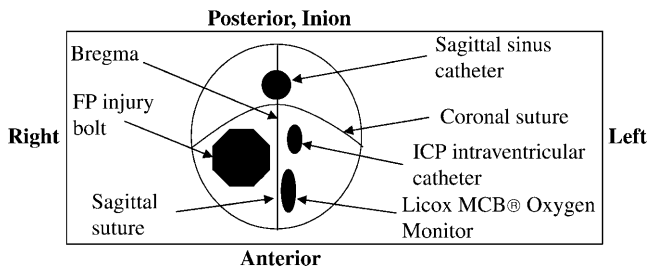
Figure 1. Diagram of pig cranium and brain instrumentation sites. FP = fluid percussion; ICP = intracranial pressure.

majority of basic science trials.[36–39] A dose of 4 mg/kg was given 10 minutes prior to injury, followed by a second dose of 2 mg/kg 1 minute prior to injury. We selected these doses based on extensive review of the literature. These doses are high enough to demonstrate clear physiologic effects, with appropriately elevated serum cocaine levels, but not large enough to lead to mortality in the absence of TBI.[38,40,41]

Halothane was used as the primary anesthetic agent because it has fewer effects on systemic and cerebral hemodynamics when compared with barbiturate or other IV anesthetics.[40,41] It is also less likely to cause apnea, and easy to titrate to level of sedation. The concentration of halothane required to maintain anesthesia is reduced when it is delivered with nitrous oxide, as described in the experimental protocol. Ketamine, with its relatively short half-life and rapid redistribution, was used for initial sedation of the animals, and is preferred over other longer-lasting agents, such as benzodiazepines. Previous modeling with sham animals subjected only to instrumentation was used to control for the confounding effects of anesthesia.

Cocaine Administration. Cocaine-treated animals (n = 7) received the first dose 10 minutes prior to injury, and a second dose 1 minute prior to injury (Figure 2). Cocaine hydrochloride, obtained from the National Institute on Drug Abuse, was diluted to a total volume of 20 mL with normal saline and administered to the right femoral vein over 1 minute. Control animals (n = 7) received 20 mL of normal saline.

Measurements. Pre-injury baseline metabolic, hemodynamic, and blood flow measurements were ob-

tained, and then repeated 10 minutes after the first cocaine dose. Traumatic brain injury was inflicted 1 minute following the second dose of cocaine or saline control bolus using a standard fluid percussion device (t = 0) (Stevenson Machine Company, Cincinnati, OH) with a target injury of 3 atm.[20] Tidal volume, respiratory rate, minute ventilation, and end-tidal carbon dioxide ($ETCO_2$) level were continuously monitored (Datex Capnomac Ultima, Datex Instrumentarium Corp., Helsinki, Finland). Figure 2 has the complete timeline. In the event of apnea, oxygen saturation less than 96%, or minute ventilation less than 2.5 L/min, the animals were provided ventilatory support via a volume-cycled ventilator (Metomatic Veterinary Ventilator, Ohio Medical Products/BOC, Murray Hill, NJ). Tidal volume and respiratory rate were adjusted to maintain arterial partial pressure of carbon dioxide (pCO_2) of 40–45 torr. Animals were observed for a total of three hours following injury. At three hours, the animals were euthanized with a lethal overdose of pentobarbital.

Heart rate, MAP, CVP, PA pressure, left ventricular pressure, ICP, respiratory rate, $ETCO_2$, minute ventilation, halothane, oxygen, nitrous oxide inspiratory concentrations, and core body and brain temperatures were continuously monitored. Cardiac output was measured via thermodilution technique at baseline and every 15 minutes until 90 minutes following injury, and then every 30 minutes thereafter. Blood was collected at baseline, at 15-minute intervals until 90 minutes post-injury, and then at 30-minute intervals thereafter for hemoglobin, hematocrit, arterial, mixed-venous, and cerebral venous blood gas measurements, and arterial and cerebral venous glucose and lactate measurements (Radiometer Medical: ABL 505, EML 100, and OSM3, Copenhagen, Denmark).

Cerebral blood flow measurements were obtained using the dye-labeled microsphere technique at baseline and at 15, 60, and 120 minutes following injury (detailed in prior studies).[19,22,23,42,43] Cerebral perfusion pressure, cerebral oxygen delivery (CDO_2), CO_2ER, and cerebral metabolic rate of oxygen consumption ($CMRO_2$) were calculated from the measured variables.[22] Blood for serum cocaine and benzoylecgonine measurements were collected at time t = 0 and t = 10. Seven milliliters of whole blood was collected in sodium fluoride- and oxalic acid-pretreated tubes to prevent cocaine hydrolysis by
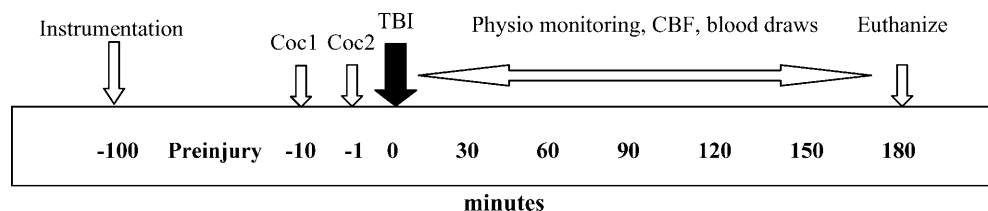
Figure 2. Experimental timeline. Coc1 = first dose cocaine (4 mg/kg IV); Coc2 = second dose cocaine (2 mg/kg IV); TBI = traumatic brain injury; CBF = cerebral blood flow.

nonspecific plasma cholinesterases, then centrifuged. The serum was adjusted to a pH of 5.5 with 10% acetic acid and the samples were then immediately frozen to −70°C. Drug levels were calculated by gas chromatography/mass spectrometry (GC/MS; National Medical Services, Inc., Willow Grove, PA).

Data Analysis. We performed a pre-hoc sample-size calculation with primary outcomes of CBF, CPP, and CO_2ER at 60 minutes post-injury. Assuming an alpha (α) value of 0.05, experimental groups of 10 animals would yield a power of 0.89 for CBF [effect size (E) = 30 mL/100 g/min, standard deviation (σ) = 20], a power of 0.80 for CPP (E = 20 mm Hg, σ = 15), and a power of 0.80 for CO_2ER (E = 0.20, σ = 0.15). Independent Student's t-test was used to determine the differences between the cocaine-administered and control animals at preselected time points. Repeated-measures analysis of variance (rmANOVA) was used for analysis of longitudinally measured parameters. p-values and 95% confidence intervals (95% CIs) are reported. Statistical analysis was completed using Systat version 10.2 (Systat Software, Inc., Point Richmond, CA).

RESULTS

Data are presented as mean (±SD). All animals survived the 180-minute observation period. Mean cocaine levels were 1,771 (±403) ng/mL at the time of injury (t = 0) and 983 (±365) ng/mL at 10 minutes following injury (t = 10). The mean injury for all animals was 3.02 (±0.30) atm. There was no statistically significant difference between the two groups in

TABLE 1. Summary of Results

|	Cocaine (n=7)	Control (n=7)	95% CI	p value
ICP (mm Hg)	11.1 (5.8)	15.4 (8.2)	−12.5, 3.9	0.18
CPP (mm Hg)	75.1 (15.9)	67.7 (14.2)	−10.1, 25.0	0.38
CBF(mL/ 100g/min)	59.6 (29.2)	53.1 (16.6)	−21.2, 34.1	0.84
RBF(mL/ 100g/min)	292.3 (35.3)	247.8 (34.8)	3.7, 85.3	0.59
$CMRO_2$(mL/ 100g/min)	356.1 (141.7)	315.4 (103)	−103.5, 185	0.55
CO_2ER	0.45 (0.18)	0.43 (0.14)	−0.17, 0.2	0.99
CVL (mEq/L)	0.91 (0.19)	1.14 (0.22)	−0.47, 0.01	0.06
Cocaine (ng/mL)	1771 (403)			

All data are mean values, with standard deviations in parentheses; reported values are at t=60 minutes, except cocaine (t=1). p-values reported are from rmANOVA comparisons between groups.
CI = confidence interval; ICP = intracranial pressure; CPP = cerebral perfusion pressure; CBF = cerebral blood flow; RBF = renal blood flow; $CMRO_2$ = cerebral metabolic rate of oxygen consumption; CO_2ER = cerebral oxygen extraction ratio; CVL = cerebral venous lactate.

any of the primary outcome measures: CPP, CBF, or CO_2ER. Although initial plans were for ten animals per group, after seven per group were completed, there was clearly no difference between groups, and the remaining animals were not sacrificed. Results are summarized in Table 1.

There was a trend toward lower ICP in cocaine-intoxicated animals, mean = 11.1 (±5.8) mm Hg vs. controls mean = 15.4 (±8.2) mm Hg at 60 minutes post-injury, although this did not reach statistical significance (p = 0.18; rmANOVA) (Figure 3). The
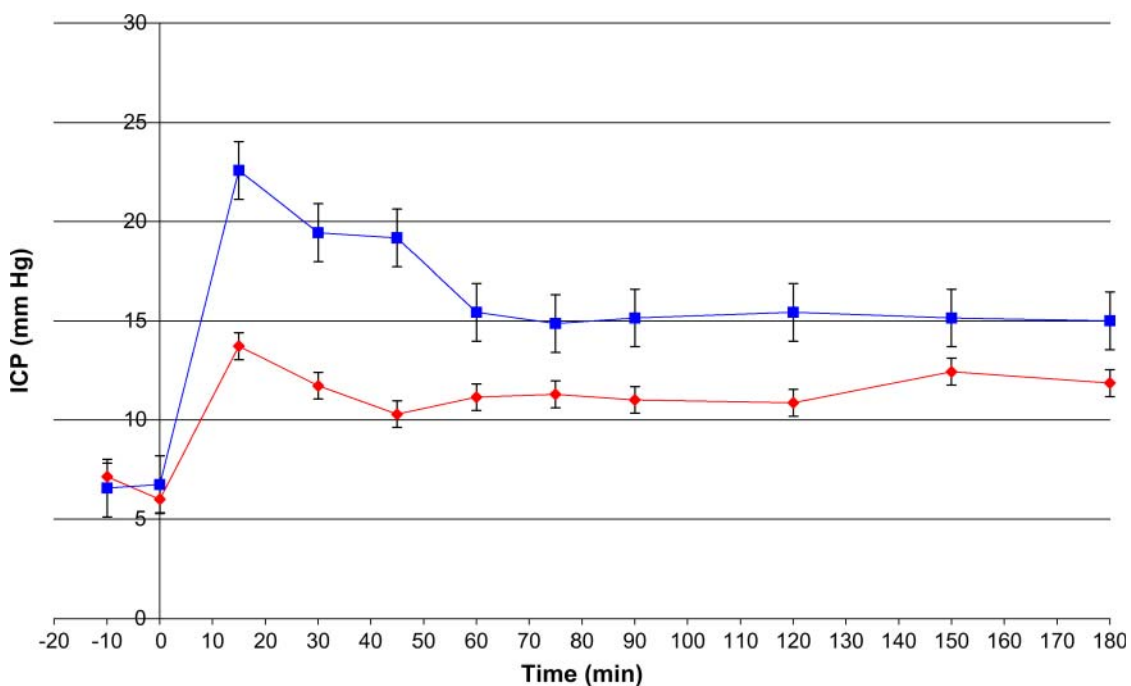
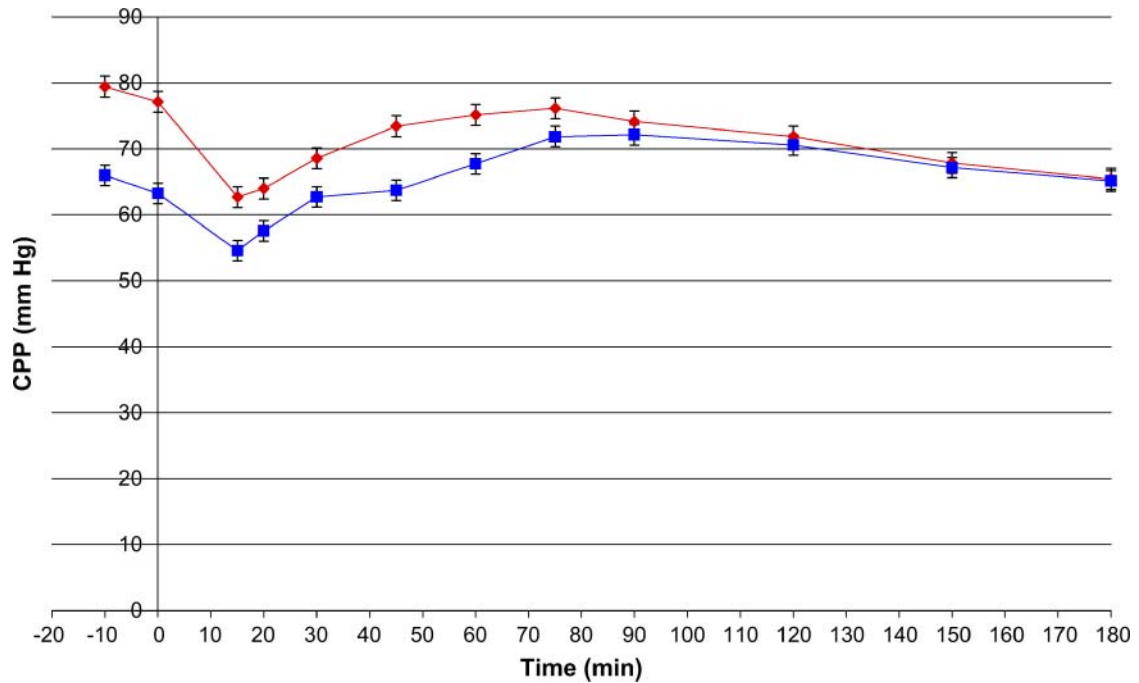**Figure 3.** Intracranial pressure (ICP). ♦, Cocaine; ■, Control.

Figure 4. Cerebral perfusion pressure (CPP). ♦, Cocaine; ■, Control.

MAPs did not differ between groups, and the trend toward lower ICP in the cocaine-administered group did not translate into improved CPP (Figure 4). Cardiac outputs were not significantly different between groups, mean = 2.23 ($\pm$0.47) L/min in cocaine-administered animals vs. 2.69 ($\pm$0.76) L/min in control animals (p = 0.12; rmANOVA). There was a trend toward lower cerebral venous lactate (CVL) levels in the cocaine-intoxicated group, mean = 0.91 ($\pm$0.19) mEq/L at t = 60, vs. the control group, mean = 1.14 ($\pm$0.22) mEq/L. This did not reach statistical significance, however (p = 0.06; rmANOVA) (Figure 5). The CBFs decreased significantly from baseline following injury in both groups, but were not significantly different between groups (Figure 6). In contrast to the CBF, the RBF did not decrease following injury (Figure 7). Although it was significantly higher in the cocaine-intoxicated animals,
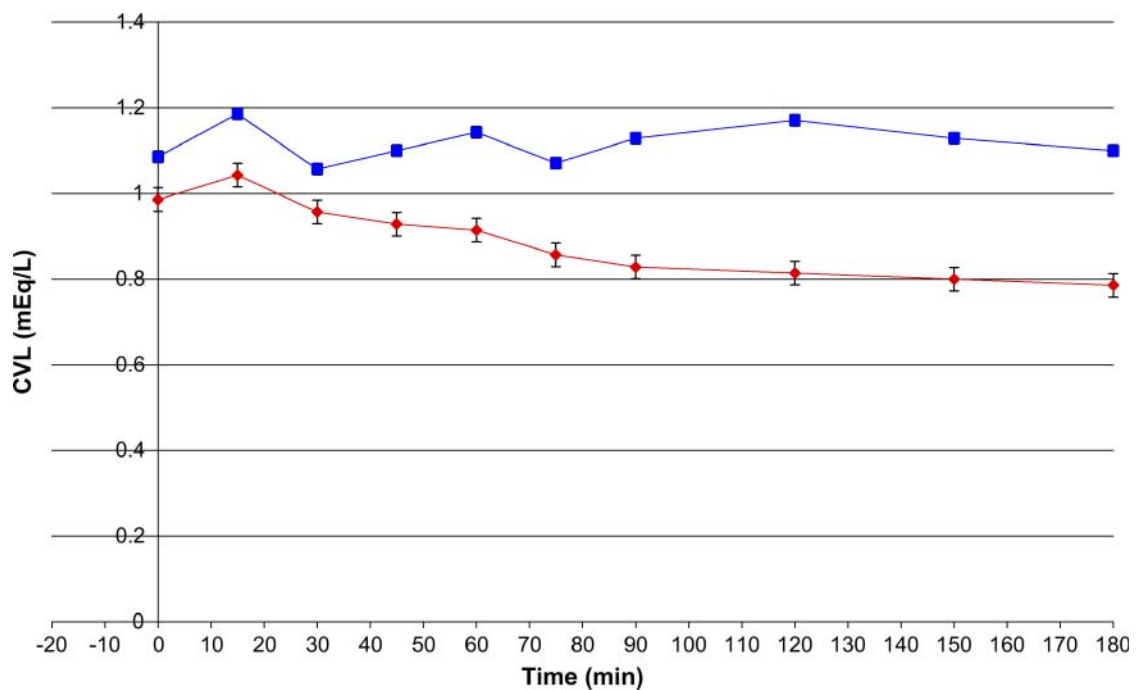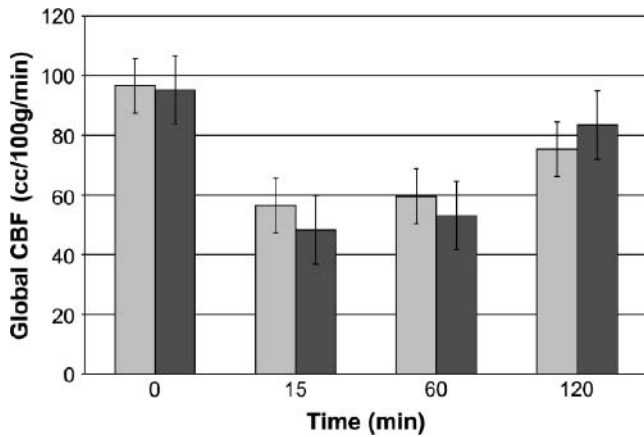

**Figure 5.** Cerebral venous lactate (CVL). ♦, Cocaine; ■, Control.

Figure 6. Global cerebral blood flow (CBF). ☐, Cocaine; ■, Control.

mean = 292.3 ($\pm$35.3) mL/100 g/min, vs. the control animals, mean = 247.8 ($\pm$34.8) mL/100 g/min, at t = 60 (p = 0.035), this was not reflected in comparisons at other time points (p = 0.59; rmANOVA). The CO_2ERs did not differ between the cocaine-intoxicated animals, mean = 0.45 ($\pm$0.18), and the control animals, mean = 0.43 ($\pm$0.14), at t = 60 or other time points compared (p = 0.99; rmANOVA). There was no significant difference in the $CMRO_2$ values between the cocaine-intoxicated group, mean = 356.1 ($\pm$141.7) mL/100 g/min, and the control group, mean = 315.4 ($\pm$103) mL/100 g/min (p = 0.55).

DISCUSSION

There have been very few studies investigating the effects of cocaine in TBI and, to the best of our knowledge, none in large animal models. This investigation sought to delineate the effects of the drug on basic physiologic and metabolic parameters in the setting of a significant injury. Overall, there was no difference in the primary outcomes of CPP, CBF, or CO_2ER. The CBF was compromised in both groups following injury, but there was no difference between groups. The RBF, which serves as a second physiologic comparison with
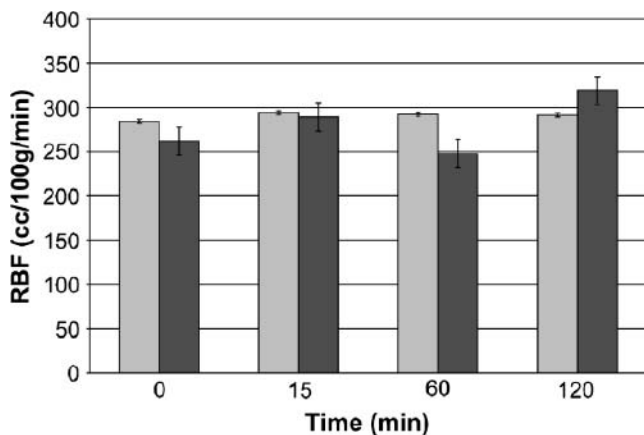
Figure 7. Renal blood flow (RBF). ☐, Cocaine; ■, Control.

CBF, was not significantly affected by brain injury in either group. It was thought that the trend toward lower ICP in the cocaine-intoxicated group was not clinically significant without a difference in any of the primary outcomes.

The cocaine dosing regimen was chosen after reviewing basic science data from prior cocaine pharmacokinetic studies in rats, dogs, and swine, and discussion with toxicologists who have done basic science research in the field.[36–39,44,45] This protocol sought to simulate the clinical scenario where a user might sustain a TBI in a motor vehicle collision while acutely intoxicated with cocaine. A dose of cocaine was chosen that would be intoxicating yet would not result in primary toxicity (cardiac arrhythmias, seizures, cardiovascular collapse) independent of TBI. Two doses in rapid succession were used to avoid primary toxicity with a single large dose, and with the expectation that serum cocaine levels would drop off rapidly as the drug was metabolized.[44,45] IV administration rather than intraperitoneal administration was selected with aims of more reliable absorption and more predictable serum levels.

There was a trend toward lower ICPs in the cocaine-intoxicated animals; the difference was more pronounced immediately after injury and became less significant further out from injury. This blunted rise in ICP was most pronounced during the time of highest serum cocaine levels. It is possible that administration of cocaine is producing effects similar to those of lidocaine, another local anesthetic that has a similar biochemical structure (cocaine is an aminoester, while lidocaine is an aminoamide).[46] Lidocaine is a commonly used adjunct to intubation in the setting of TBI and has been shown to blunt increases in ICP in this setting.[47] Lidocaine has also been shown to decrease $CMRO_2$ in certain dog models, although we did not observe an effect with cocaine in our model.[48,49] The etiology of cocaine's effect on ICP is not clear, but possible hypotheses include blockage of sodium channels or an effect on the neurotransmitter level, related to reuptake inhibition of dopamine, serotonin, or norepinephrine. Although it is possible that increased cerebral vasoconstriction due to elevated norepinephrine or dopamine may decrease CBF, and subsequently lower ICP, this was not demonstrated in this model.

The CVL was also lower in the cocaine-treated animals, although this did not reach statistical significance. In past models, elevated levels of CVL have been shown to be surrogate markers for more severe injuries, most notably in the setting of concurrent ethanol intoxication and hemorrhagic shock.[19,22] As an isolated marker of brain injury severity, lower CVL levels are not enough to infer a neuroprotective effect from cocaine, especially in the absence of any significant differences in CBF or CO_2ER. Also, the differences between very low CVL levels (well less

than 2.0 mEq/L) are unlikely to have any clinical significance.

Although there were trends toward lower ICP and CVL in the cocaine-treated animals, there was no difference in the primary outcomes of CPP, CBF, and CO_2ER. Therefore, in this model, cocaine intoxication did not have a deleterious or beneficial effect on TBI.

The relevance of this basic science study lies with the frequency of TBI as a presentation to most EDs. A good understanding of the pathophysiology of brain injury is needed to properly stabilize these patients, and this is difficult to study in the clinical setting. A significant subset of TBI patients will have concurrent intoxication, which can affect their physiologic and metabolic responses to medical and surgical interventions. Cocaine intoxication is not an infrequent finding in this group of patients, and may predispose them to unintentional trauma such as TBI. Although this investigation did not demonstrate a significant difference in any of the primary outcome measures, it represents the beginning of an attempt to investigate and better understand the complexities of cocaine intoxication and TBI. Given the trend toward lower ICP in intoxicated animals, it is possible that a beneficial effect would have been demonstrated with a lower cocaine dose or an examination of different outcome measures (neurologic function). Future endeavors may include altering the cocaine dose administered, incorporating chronic cocaine exposure to the model, and performing neurologic functional testing and survival studies. These outcomes may be more directly relevant to the human experience of cocaine and TBI, and may help someday to direct treatment both in the ED and later in the recovery and rehabilitation phases of injury.

LIMITATIONS

There are a number of limitations to this model and investigation. This was a model of acute cocaine toxicity, and cocaine also has chronic deleterious effects on cardiovascular and cerebrovascular anatomy and physiology. In the clinical setting, acute intoxication with a history of chronic use would be a more common presentation than acute intoxication without prior use.

Additionally, IV administration of cocaine may not replicate precisely intoxication by intranasal or inhalational routes used more commonly in humans. Intravenous administration leads to rapid and reproducible serum levels, but there is potential for differences in injured brain response in the setting of different routes of administration. Specifically, one might hypothesize to see slower onset of effect but more prolonged toxicity from an intranasal or inhalational exposure.

This model is also limited by the duration of observation. The animals were observed for three hours

and there was no assessment of neurologic function. Hence, this study cannot rule out the possibility of differences in long-term neurologic outcome or morbidity, or even longer-term mortality.

Although the study was conclusively negative for the primary endpoints, there was a trend toward lower ICP in the cocaine-intoxicated animals. The study was underpowered to demonstrate such an effect, and a larger study may have demonstrated a statistically significant difference.

Finally, there is potential for a neuroprotective effect from the anesthesia. Although halothane has the potential to increase ICP by causing cerebral vasodilation, it was selected specifically because it is believed to have less of a protective effect when compared with isoflurane or barbiturate anesthesia.[50–52]

CONCLUSIONS

To the best of our knowledge, this is the first study of the effects of acute cocaine intoxication in a large animal model of fluid percussion TBI. In this model, acute cocaine intoxication did not have any deleterious effects on the measured physiologic parameters. Further investigation is needed in this area to better understand the complex interactions of cocaine with the injured brain.

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