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Total Intravenous Anesthesia Including Ketamine versus *Volatile Gas Anesthesia for Combat-related Operative Traumatic Brain Injury*

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Background: **Traumatic brain injury is a leading cause of death and severe neurologic disability. The effect of anesthesia techniques on neurologic outcomes in traumatic brain injury and potential benefits of total intravenous anesthesia (TIVA) compared with volatile gas anesthesia (VGA), although proposed, has not been well evaluated. The purpose of this study was to compare TIVA *versus* VGA in patients with combat-related traumatic brain injury.**

Methods: **The authors retrospectively reviewed 252 patients who had traumatic brain injury and underwent operative neurosurgical intervention. Statistical analyses, including propensity score and matched analyses, were performed to assess differences between treatment groups (TIVA *vs.* VGA) and good neurologic outcome.**

Results: **Two hundred fourteen patients met inclusion criteria and were analyzed; 120 received VGA and 94 received TIVA. Good neurologic outcome (Glasgow Outcome Score 4–5) and decreased mortality were associated with TIVA compared with VGA (75% *vs.* 54%; $P = 0.002$ and 5% *vs.* 16%; $P = 0.02$, respectively). Multivariate logistic regression found admission Glasgow Coma Scale score of 8 or greater (odds ratio, 13.3; $P < 0.001$) and TIVA use (odds ratio, 2.3; $P = 0.05$) to be associated with good neurologic outcomes. After controlling for confounding factors using propensity analysis and repeated one-to-one matching of patients receiving TIVA with those receiving VGA with regard to Injury Severity Score, Glasgow Coma Scale score, base deficit, Head Abbreviated Injury Score, and craniectomy or craniotomy, the authors could not find an association between treatment and neurologic outcome.**

Conclusion: **Total intravenous anesthesia often including ketamine was not associated with improved neurologic outcome compared with VGA. Multiple confounders limit conclusions that can be drawn from this retrospective study.**

TRAUMATIC brain injury (TBI) affects more than 1.4 million patients each year in the United States.[1–3] Approximately 50,000 of those patients die.[1] In the survivors, TBI confers a high burden on quality-adjusted life years. The Centers for Disease Control and Prevention estimates that at least 5.3 million Americans currently have long-term or lifelong need for help to perform activities of daily living as a result of a TBI.[4] The cost associated with TBI in the United Sates is estimated to exceed $100 billion dollars annually.[5]

In addition, recent US military operations have produced unprecedented numbers of combat casualties with TBI.[6] Combat-related mortality from TBI during the Vietnam conflict and Operation Iraqi Freedom accounts for more than one third of all deaths.[6,7] Improved survival attributed to personal protective equipment and trauma care has resulted in increased numbers of patients with severe neurologic disability.[6] Strategies that improve TBI-related mortality and long-term neurologic outcomes could profoundly affect the management of TBI.[8] New therapeutic strategies, highlighted by recent studies, reveal novel insights into the pathophysiology and importance of prevention as well as treatment of secondary brain injury.[8–10]

The etiology of secondary brain injury and neuronal death includes ischemia, cerebral edema, and inflammation. This multifactorial injury is attributed to the release of excitatory mediators, cytokines, free radicals, hyperglycemia, hypoxemia, hypotension, hyperthermia, increased intracranial pressure (ICP), decreased cerebral blood flow (CBF), and decreased cerebral perfusion pressure (CPP).[8–10] To decrease secondary brain injury, prehospital and emergency medicine providers focus on the prevention and treatment of hypoxemia and hypotension. Perioperatively, neurosurgeons and intensivists commonly manage increases in ICP, decreases in CBF, and decreases in CPP, as well as provide other supportive therapies. Although the care of these patients is complex and requires a comprehensive multidisciplinary approach, little human research has evaluated the effects of anesthesia on neurologic outcomes.[8,11] Furthermore, the recent National Institutes of Health workshop and review of head injury trauma trials failed to mention the potential role of anesthetic management on neurologic outcomes.[8]

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Strategies for preventing and treating secondary brain injury in TBI patients are similar regardless of location: emergency department, intensive care unit, or operating room. Uniquely, however, the anesthesia provider is confronted with balancing and managing the effects of the anesthetic, which can exacerbate or improve secondary brain injury.[11] Volatile gas anesthetics (VGAs) have previously been shown to provide neuroprotection, although they are also associated with decreased CPP, increasing CBF, and decreasing cerebral metabolic rate for oxygen ($CMRO_2$), resulting in net adverse changes in the $CMRO_2$/CBF ratio.[12–14] Compared with VGAs, some intravenous anesthetics may possess more ideal characteristics for neuroanesthesia. These intravenous anesthetics can also decrease CPP but have also been shown to preserve CBF and cerebral vasoconstriction and reduce ICP as well as $CMRO_2$.[15] Moreover, recent studies demonstrate that many intravenous anesthetics attenuate or modulate the systemic inflammatory cascade as well as provide neuronal protection against ischemia and apoptosis.[16,17]

As a result of the positive effects associated with intravenous anesthesia, some experts consider total intravenous anesthesia (TIVA) to be the anesthetic of choice for neurosurgical procedures, although comparative outcome data in humans is lacking. Interestingly, one intravenous anesthetic, ketamine, which is commonly used in trauma to maintain hemodynamic stability, is thought to be contraindicated in TBI.[18] Recent literature, however, disputes adverse neurologic effects attributed to ketamine.[18–20] Ketamine is potentially useful for systemic hypovolemic hemorrhage seen in combat-related TBI by providing hemodynamic stability and, through *N*-methyl-D-aspartate receptor antagonism, neuroprotection.[18,21] Ketamine administration in TBI, however, continues to remain controversial.

Secondary to the paradigm shift in the literature, established goals to prevent secondary brain injury, complexity of combat-related injuries, and provider experience with the TIVA technique in austere conditions, some military anesthesia providers have used TIVA for combat-related TBI. As a result of the proposed mechanisms and anecdotal reports from military providers, we hypothesized that patients requiring neurosurgical intervention for TBI had improved neurologic outcome and mortality when TIVA was administered compared with VGA.

Materials and Methods

After approval from the institutional review board, Department of Clinical Investigation, Brooke Army Medical Center, San Antonio, Texas, we retrospectively reviewed the Joint Theater Trauma Registry for all patients

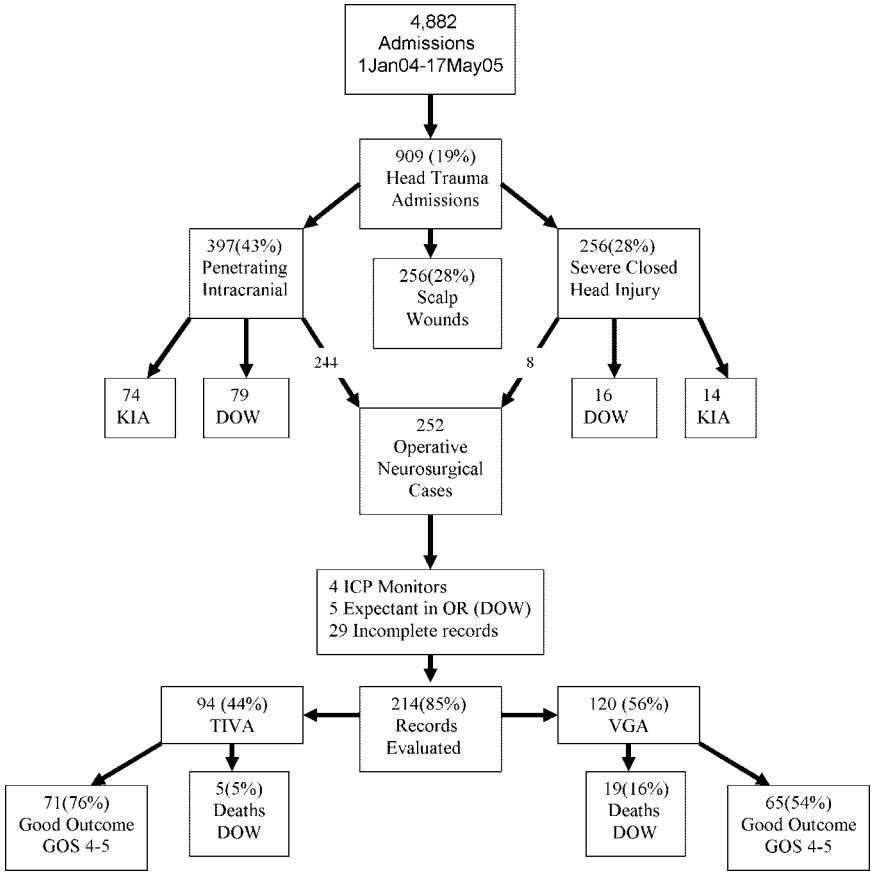

Fig. 1. Incidence of head trauma during the study period and distribution of traumatic brain injury necessitating neurosurgical intervention. Patients who received total intravenous anesthesia (TIVA) *versus* volatile gas anesthesia (VGA) with complete data were evaluated for mortality and good neurologic outcome (Glasgow Outcome Score [GOS] 4–5). DOW = died of wounds (patients surviving to combat support hospital but died after receiving some medical interventions; interventions include expectant management in patients with severe injuries); ICP = intracranial pressure; KIA = killed in action (died before reaching the combat support hospital); OR = operating room.

presenting to one combat support hospital (CSH) treated between January 31, 2004, and May 1, 2005 (n = 4,882) (fig. 1).

Data included elements of the Joint Theater Trauma Registry as well as elements from inpatient and operative records such as mechanisms of injury, treatment at aide stations (level 1), forward resuscitative surgical suite (level 2), forward surgical teams (level 2), vital signs, and treatment at the CSH (level 3). Treatment and data from the CSH included type of surgery, duration of surgery, location of surgery, type of anesthesia, intraoperative anesthetic record, admission base deficit, arterial pH, serum glucose concentration, blood products administered during hospital course, intensive care unit duration of stay, ventilator days, number of days at level 3, and Injury Severity Score (ISS). For American casualties evacuated out of the theater of operations to Landstuhl Regional Medical Center (level 4) or military treatment facilities in the continental United States (level 5), data included ventilator days, intensive care unit days, and hospital days. The admission Glasgow Coma Scale (GCS) score was determined by using the best GCS score recorded from the scene or at level 1, 2, or 3. Craniectomy or craniotomy was performed at the discretion of the neurosurgeon based on type of skull injury, severity of injury, and intraoperative evidence of cerebral edema. Glasgow Outcome Score (GOS) using standard criteria (appendix) was determined at the time of hospital discharge. A total of three neurosurgeons performed all procedures and had similar practices. Anesthesia care was delivered primarily by two providers, both with similar anesthetic goals. The goals included preventing secondary brain injury by decreasing ICP, cerebral edema, and $CRMO_2$; maintaining hemodynamic stability and perfusion pressure; and avoiding hypoxemia and hyperglycemia. Providers, for example, specifically attempted to maintain hemoglobin greater than 10 g/dl, systolic blood pressure (SBP) greater than 90 mmHg, glucose less than 150 mmol/dl, partial pressure of arterial carbon dioxide ($Paco_2$) 33–35 mmHg, and partial pressure of arterial oxygen (Pao_2) greater than 100 mmHg; treat coagulopathy; minimize positive end-expiratory pressure; and maintain slight hypothermia (36°C) or normothermia.

In this study, two treatment groups for comparison included patients who received neurosurgical intervention with VGA or TIVA. These patients were not randomized to treatment or selected based on presentation. All patients presenting before August 21, 2004, received VGA. On August 21, 2004, neuroanesthesia providers started using TIVA techniques with anecdotal improvements in hemodynamic changes and operating conditions secondary to decreased cerebral edema. After August 21, 2004, 11 patients received VGA performed by anesthesia providers not on the neuroanesthesia team, whereas all others treated after this date received TIVA. As a result, treatment groups were nearly completely confounded by temporal period. Treatment selection was based solely on anesthesia provider preference and date of admission. The majority of patients received perioperative phenytoin, mannitol, and antibiotics. Balanced VGA included an opioid consisting of fentanyl or sufentanil and either sevoflurane or isoflurane. End-tidal volatile gas monitoring was not available. The TIVA techniques used propofol (75–150 $\mu g\ kg^{-1}\ min^{-1}$) combined with remifentanil (0.05–0.3 $\mu g\ kg^{-1}\ min^{-1}$), sufentanil (0.001–0.002 $\mu g\ kg^{-1}\ min^{-1}$), or fentanyl (0.01–0.02 $\mu g\ kg^{-1}\ min^{-1}$) and sometimes ketamine (5–20 $\mu g\ kg^{-1}\ min^{-1}$). Sodium thiopental was administered for cerebral edema at the discretion of the neurosurgeon. The primary outcome in our study was good (GOS 4–5) or bad (GOS 1–3) neurologic outcome at time of hospital discharge. In addition, subset analysis was performed on the TIVA group comparing those patients who received ketamine *versus* no ketamine.

Statistical Analysis

Demographic and clinical characteristics are presented as proportion for categorical variables, median (interquartile range) for nonparametric analysis using the Wilcoxon test, and mean ± SD for parametric analysis using analysis of variance. Groups were contrasted on binary outcomes with Pearson chi-square or Fisher exact test as appropriate. In an attempt to eliminate confounding by temporal period, treatment groups were contrasted on good neurologic outcome by application of the McNemar test[22] and matched-pair odds ratio after repeated one-to-one matching of patients receiving TIVA with those receiving VGA with regard to ISS (to within 10%), and perfectly on GCS (< 8, ≥ 8), base deficit (< 6, ≥ 6), Head Abbreviated Injury Score (≤ 3,> 3) and craniectomy *versus* craniotomy. From these, subsets of approximately 30 matched pairs were selected without replacement 100 times, and the 100 matched-pair odd ratios and *P* values relating treatment (TIVA, VGA) and good neurologic outcome (bad, good) were saved; the median and range of the 100 odds ratios and 100 *P* values were reported. An unmatched treatment group contrast on good neurologic outcome was made with adjustment for a propensity score. Because treatment was not based on presurgical clinical characteristics, a modified propensity analysis was performed to adjust for injury severity. The variables we used to index injury severity were the craniectomy/craniotomy, hematocrit, and surgical time. A logistic model for treatment was applied in terms of these three variables. The propensity score, defined as the prediction probability from the logistic model, was used to adjust for injury severity in modeling good neurologic outcome from treatment, base deficit, and GCS. All statistical testing was two-sided, with a significance level of 5%, and SAS version 9.1 for Windows (SAS Institute, Cary, NC) was used throughout.

Table 1. Demographics and Admission Vital Signs/Laboratory Data

	VGA, n = 120	TIVA, n = 94	*P* Value
Age,* yr	27 ± 12	27 ± 9	0.96
Coalition forces	68/120 (57%)	51/94 (54%)	0.73
Iraqi or noncoalition	52/120 (43%)	43/94 (46%)	0.73
Mechanism of injury			
GSW	30/116 (25%)	22/77 (29%)	0.65
Blast	75/116 (64%)	44/77 (57%)	0.33
MVC	11/116 (9%)	11/77 (14%)	0.29
Polytrauma	39/120 (32%)	25/94 (26%)	0.35
Level 1 or 2 intervention	46/120 (38%)	36/94 (38%)	0.70
Intubation in field/ED	77/118 (65%)	54/93 (58%)	0.32
Admission SBP,* mmHg	126 ± 26	132 ± 24	0.1
SBP < 90 mmHg	9/120 (8%)	3/94 (4%)	0.24
Admission temp,† °F	96.8 (94.2–98.7)	96.5 (95.1–97.8)	0.53
Temp < 95°F	36/118 (31%)	20/93 (21%)	0.16
$Paco_2$,* mmHg	38 ± 9	39 ± 11	0.26
Sodium,* mM	137 ± 5	136 ± 6	0.76
Glucose,† mg/dl	149 (119–179)	142 (114–181)	0.49
INR†	1.4 (1.2–1.5)	1.3 (1.1–1.4)	0.02
Platelets,† mm^3	217 (150–247)	234 (181–290)	0.04
Hematocrit,* %	34.8 ± 7.6	38.3 ± 6.9	< 0.001
pH*	7.33 ± 0.13	7.36 ± 0.09	0.07
Base deficit†	3 (0–6)	2 (0–4)	0.01
Base deficit ≤ −6	31 (28%)	16 (18%)	0.13
ISS 98†	25 (15–27)	25 (16–29)	0.65
Head AIS 2–3	21 (20.2%)	12 (17.1%)	
Head AIS 4	32 (30.8%)	24 (34.3%)	
Head AIS 5	51 (49%)	34 (48.6%)	
GCS†	9 (6–14)	11.5 (6–14)	0.31
GCS score ≥ 8	62 (52%)	58 (63%)	0.12
Heart rate,* beats/min	93.5 ± 24.3	83.8 ± 23.6	0.004
Operative time,* min	234.5 ± 97.7	182.1 ± 17.4	<0.001

* Data expressed as mean ± SD. Used for parametric analyses. † Data expressed as median and interquartile range. Used for nonparametric analyses.

ED = emergency department; GCS = Glasgow Coma Scale; GSW = gunshot wound; Head AIS = Head Abbreviated Injury Score; INR = international normalized ratio; ISS 98 = Injury Severity Score 1998; level 1 or 2 = refers to military levels below level of combat support hospital level 3, *e.g.*, buddy aide, battalion aide stations, forward surgical teams; MVC = motor vehicle crash; $Paco_2$ = arterial carbon dioxide tension; polytrauma = more than one injury; SBP = systolic blood pressure; SBP < 90 mmHg = number of patients presenting with systolic blood pressure less than 90 mmHg; temp = temperature; TIVA = total intravenous anesthesia; VGA = volatile gas anesthesia.

Results

Review of the Joint Theater Trauma Registry revealed that 19% of patients (909/4,882) sustained traumatic head injury (fig. 1). Two hundred fifty-two TBI patients had neurosurgical interventions. Patients who underwent ICP monitor placement only (n = 4) or were not expected to survive the operation (n = 5) because of devastating injury determined intraoperatively by the attending neurosurgeon were excluded. Records were stored and maintained by the CSH patient administration, and after redeployment they were transported to the Patient Administration Systems and Biostatistics Activity (Fort Sam Houston, Texas), where they were subsequently scanned into PDF form. Complete records and follow-up data were unavailable for 12% (29/243). Twenty of the 29 patients (69%) had entire charts that could not be located, which limited our ability to meaningfully compare groups and outcomes. The remainder of missing data (9/29, 31%) included partial missing records and documentation of neurologic outcome, which was evenly distributed in both TIVA (4/9) and VGA (5/9) groups. Of the remaining 214 patients, 120 were anesthetized with VGA and 94 were anesthetized with TIVA. Demographic data are presented in table 1. We performed a nonmissing value analysis for each variable, and review of those data suggested that missing values were relatively balanced between the two groups among the subjects actually included in the analysis. Patients receiving VGA exhibited increased mean heart rate (± SD) (VGA: 93.5 ± 24.3 beats/min, TIVA: 83.8 ± 23.6 beats/min; $P = 0.004$), decreased mean hematocrit (VGA: 34.7 ± 7.6, TIVA: 38.3 ± 6.9; $P < 0.001$), and increased median international normalized ratio (VGA: 1.4, TIVA: 1.3; $P = 0.02$). Despite the statistical differences, groups seemed clinically similar for admission vital signs and laboratory data.

Table 2 summarizes intraoperative data and postoperative outcomes between the two treatment groups, VGA *versus* TIVA. Clinically and statistically significant differences included mean surgical time (VGA: 235 ± 98 min, TIVA: 182 ± 71 min; $P < 0.001$), mean amount of crystalloid administered (VGA: 2.7 ± 1.4 l, TIVA: 3.5 ±

Table 2. Intraoperative Data and Postoperative Outcomes

	VGA, n = 120	TIVA, n = 94	*P* Value
Lowest SBP,* mmHg	97 ± 10	108 ± 9	< 0.001
Change in SBP,* mmHg	19 ± 11	11 ± 6	< 0.001
Surgical time,* min	235 ± 98	182 ± 71	< 0.001
Erythrocytes given	74/120 (62%)	49/94 (52%)	0.14
FFP given	64/120 (51%)	29/94 (30%)	0.002
Factor VIIa (intraop)	9/119 (8%)	8/94 (9%)	0.8
Crystalloid,* l (intraop)	2.7 ± 1.4	3.5 ± 1.5	< 0.001
Urine output,† l (intraop)	1.1 (0.6–1.9)	1.2 (0.6–2.0)	0.58
Intraoperative ET_{CO_2}*	27 ± 4	27 ± 3	0.54
Craniectomy	71/119 (60%)	25/94 (27%)	< 0.001
ICP monitor placed	63/119 (53%)	46/91 (50%)	0.29
Total vent days†‡	2 (1–6)	2 (0–6)	0.31
Total ICU days†‡	5 (3–10)	5 (2–9)	0.19
Total hospitalization days†‡	10 (5–24)	8 (4–16)	0.21
GOS*	3.4 ± 1.4	4 ± 1.2	0.001
Good outcome GOS (4–5)	65/120 (54%)	71/94 (75%)	0.002
Day GOS measured†	10 (5–24)	7 (4–16)	0.21
Death	19/120 (16%)	5/94 (5%)	0.02

* Data expressed as mean ± SD. Used for parametric analyses. † Data expressed as median and interquartile range. Used for nonparametric analyses. ‡ Data only includes patients who survived.

Change in SBP = maximal > 5 min sustained change in systolic blood pressure; day GOS measured = day Glasgow Outcome Score determined, usually at hospital discharge; erythrocytes given = erythrocyte transfusion administered intraoperatively; factor VIIa = factor VII activated; FFP given = fresh frozen plasma administered intraoperatively; GOS = Glasgow Outcome Score; ICP = intracranial pressure; ICU = intensive care unit; intraop = intraoperatively; intraoperative ET_{CO_2} = average steady state end-tidal carbon dioxide; SBP = systolic blood pressure; TIVA = total intravenous anesthesia; VGA = volatile gas anesthesia.

1.5 l; $P < 0.001$), percentage with craniectomy (VGA: 60%, TIVA: 27%; $P < 0.001$), average hospital days (VGA = 12 and TIVA = 8; $P = 0.04$), mean GOS (VGA: 3.4 ± 1.4, TIVA: 4 ± 1.2; $P = 0.001$), good neurologic outcomes (GOS 4–5) (VGA: 54%, TIVA: 75%; $P = 0.002$), and risk of death (VGA: 16%, TIVA: 5%; $P = 0.02$) in VGA relative to TIVA. The discharge GOS was documented for VGA patients on average on day 10 (5–24) and for TIVA on day 7 (4–16) ($P = 0.21$). Although lowest SBP, change in SBP, and fresh frozen plasma use showed statistically significant differences between VGA and TIVA groups, none was thought to be clinically significant. In addition, the same analysis compared patients admitted before August 21, 2004, with those admitted on or after August 21, 2004. This is the date TIVA was first delivered. As expected because only 11 patients received VGA after August 21, the analysis mirrored the comparisons of VGA *versus* TIVA.

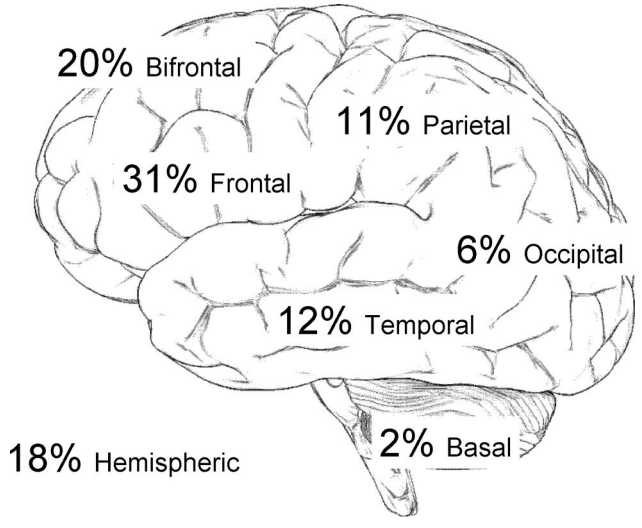

Fig. 2. Average anatomical distribution of surgical intervention. The two treatment groups were similar with regard to the anatomical locations of interventions. Injury location associated with the highest percent of mortality was right occipital (3/21, 14%) and left hemispheric (7/21, 33%).

Figure 2 demonstrates the percentage of neurosurgical procedures performed by anatomical location. There were no differences ($P = 1.0$) in the percentage of right-sided (VGA: 52/88, 59%; TIVA: 36/88, 41%) or left-sided (VGA: 44/75, 59%; TIVA: 31/75, 41%) injury or procedures, although there were more bifrontal procedures in the TIVA group (24/40, 26%). Injury locations associated with the highest percent mortality were right occipital and left hemispheric.

A multivariate logistic regression model of good neurologic outcome (table 3), unadjusted for craniectomy *versus* craniotomy, revealed that the odds of a good outcome were increased for subjects receiving TIVA (odds ratio, 2.32; 95% confidence interval, 0.99–5.45; $P = 0.05$), but the odds of a good outcome with TIVA were not significantly increased (odds ratio, 1.49; 95% confidence interval, 0.58–3.81) after additional adjustment for craniectomy *versus* craniotomy and surgical time (table 4).

Treatment was confounded with temporal period; 90.8% (109/120) of patients receiving VGA were admitted before August 21, 2004, whereas 100% of patients receiving TIVA and 9.2% (11/120) of VGA patients were admitted on or after that date. Before August 21, 2004 (VGA group) was associated with markers of injury that

Table 3. Logistic Regression Model for GOS 4–5 Outcome Unadjusted for Craniectomy *versus* Craniotomy

Variable	Odds Ratio	95% CI	*P* Value*
TIVA *vs*. VGA	2.32	(0.99–5.45)	0.05
Hematocrit	1.06	(1–1.13)	0.04
ISS 98	1.03	(0.99–1.07)	0.14
INR	0.16	(0.03–0.78)	0.02
GCS 8 (above 8 *vs* . below 8)	13.32	(5.8–30.56)	< 0.001

* *P* value from Wald chi-square test.

CI = confidence interval; GCS 8 = Glasgow Coma Scale score ≥ 8; ISS 98 = Injury Severity Score 1998; GOS 4–5 = Glasgow Outcome Score, good outcome; INR = international normalized ratio; TIVA = total intravenous anesthesia; VGA = volatile gas anesthesia.

may demonstrate increased severity of injury. These include increased mean heart rate (pre: 93.3 ± 25.2 beats/min, post: 85.2 ± 23 beats/min; $P = 0.02$), decreased hematocrit (pre: 35.1 ± 7.3, post: 37.5 ± 7.6; $P = 0.02$), increased operative time (pre: 235.3 ± 92.9 min, post: 186.9 ± 81.7 min; $P < 0.001$), decreased crystalloid (pre: 2.7 ± 1.4 l, post: 3.4 ± 1.6 l; $P < 0.001$), increased mean international normalized ratio (pre: 1.4 ± 0.3, post: 1.3 ± 0.3; $P = 0.006$), increased risk of bad GOS (1–3) (pre: 45.4%, post: 27.4%; $P = 0.007$), and increased risk of death (pre: 15.7%, post: 6.6%, $P = 0.05$).

Attempts to eliminate potential biases caused by confounding with temporal period were made by (1) a modified propensity score analysis and (2) matching on injury severity and four other variables. One hundred fifty-four patients (TIVA: 60, VGA: 94) had complete data for the five matching variables (ISS, GCS [< 8, ≥ 8], base deficit [< 6, ≥ 6], Head Abbreviated Injury Score [≤ 3, > 3], and craniectomy/craniotomy). After matching, 40 distinct matched pairs were found. From these, 30 matched pairs were selected without replacement 100 times. The median odds ratio relating treatment with neurologic outcome was 1.24 (range, 0.31–6.5), with a median *P* value of 0.56 (range, 0.13–1.0). In a separate analysis, treatment was not associated with good neurologic outcome after adjustment for propensity score (odds ratio, 1.21; 95% confidence interval, 0.5–2.75; $P = 0.65$).

Table 4. Logistic Regression Model for GOS 4–5 Outcome Adjusted for Surgical Time and Craniectomy *versus* Craniotomy

Variable	Odds Ratio	95% CI	*P* Value*
TIVA *vs*. VGA	1.49	(0.58–3.81)	0.41
Craniectomy *vs*. craniotomy	0.39	(0.17–0.91)	0.03
Hematocrit	1.06	(1–1.12)	0.06
Surgical time	1	(0.99–1)	0.12
ISS 98	1.03	(0.99–1.07)	0.16
INR	0.16	(0.03–0.77)	0.02
GCS 8 (above 8 *vs*. below 8)	12.23	(5.24–28.56)	< 0.001

* *P* value from Wald chi-square test.

CI = confidence interval; GCS 8 = Glasgow Coma Scale score ≥ 8; GOS 4–5 = Glasgow Outcome Score, good outcome; ISS 98 = Injury Severity Score 1998; INR = international normalized ratio; TIVA = total intravenous anesthesia; VGA = volatile gas anesthesia.

Table 5. TIVA Subgroup Analysis Comparing Clinically Significant Admission Data, Injury Severity, and Outcomes in Groups with Ketamine *versus* No Ketamine

	No Ketamine, 46/93 (50%)	Ketamine, 47/93 (50%)	*P* Value
ISS 98†	25 (17–27)	25 (14–30)	0.60
Admission SBP,* mmHg	130 ± 20	133 ± 27	0.51
Lowest intraoperative SBP,† mmHg	105 (100–115)	105 (100–110)	0.83
Admission GCS score†	11 (7–15)	13 (6–15)	0.97
Base deficit†	2 (0–5)	2 (0–3)	0.54
Glucose,† mg/dl	147 (119–186)	133 (102–178)	0.18
Temperature,* °F	96.6 ± 2	96.2 ± 2	0.35
GOS†	4 (3–5)	4 (4–5)	1.0
Good outcome GOS (4–5)	33/46 (72%)	37/47 (79%)	0.47
Mortality	1/46 (2.2%)	4/47 (8.5%)	0.36‡

* Data expressed as mean ± SD. Used for parametric analyses. † Data expressed as median and interquartile ranges. Used for nonparametric analyses. ‡ Fisher exact test.

GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Score; ISS 98 = Injury Severity Score 1998; SBP = systolic blood pressure; TIVA = total intravenous anesthesia.

A subgroup analysis (table 5) was performed on the TIVA group to evaluate the effects of ketamine. No patients in the VGA group received ketamine. In the TIVA group, median ISS did not vary significantly with the use of ketamine (ketamine: 25, no ketamine: 25; $P = 0.60$), and ketamine use was not significantly associated with death (ketamine: 8.5%, no ketamine: 2.2%; $P = 0.36$) or good neurologic outcome (GOS 4–5) (ketamine: 79%, no ketamine: 72%; $P = 0.47$).

Discussion

This retrospective study did not support our hypothesis. We could not demonstrate a significant difference in neurologic outcomes in patients with TBI requiring neurosurgical intervention when TIVA was compared with VGA. Specifically, when modified propensity scores were used to adjust for potential differences in injury severity and eliminate confounding factors such as admission hematocrit, SBP, and base deficit, which were associated with and predictors of neurologic outcomes and mortality, no differences were found. Conversely, TIVA including ketamine in a majority of patients seemed at least as efficacious and safe as VGA in these severely injured patients. This work supports the need and feasibility to perform prospective evaluations comparing TIVA *versus* VGA in severe TBI. Although VGAs have been compared with propofol in animal head injury models, this study is the first human outcome study comparing VGA with TIVA for TBI requiring neurosurgical intervention.[12–17]

The long history and reported safety of VGAs for neuroanesthesia in humans supports their use.[11] In addition, volatile gases are thought to be particularly useful for

neurosurgical anesthesia because they decrease $CMRO_2$, attenuate surgical stimulation, provide neuroprotection, and allow rapid emergence. When administered prophylactically, recent studies suggest neuronal protection is conferred.[23] Although these properties support VGA use, they are also associated with many disadvantages, which drive efforts to discover superior anesthetics. Disadvantages associated with the VGAs include cerebral vasodilatation, increased CBF, increased cerebral blood volume, increased ICP, and cerebral steal syndrome.[12–14] VGAs also impair cerebral autoregulation in a dose-dependent fashion, creating increased dependence on CPP for blood flow.[24,25] As a result, decreases in mean arterial pressure (MAP) overwhelm vascular compensatory mechanisms and CBF decreases.[26,27] Finally, all volatile agents decrease systemic blood pressure and depress myocardial function in a dose-dependent manner, both of which exacerbate decreases in MAP and subsequently lower CPP.[28]

Many experts recommend a propofol-based TIVA for neuroanesthesia because many of the adverse effects associated with VGAs are eliminated.[15] In a rat model of TBI with moderate hypothermia, propofol preserved ICP, CPP, and MAP better than isoflurane.[29] In addition, propofol was found to have neuroprotective properties.[16,30–32] Similar to the VGAs, propofol decreases $CMRO_2$, but unlike the VGAs, propofol also preserves CBF, produces cerebral vasoconstriction reducing cerebral blood volume, and reduces ICP.[27,33] Cerebral blood volume reduction in neurosurgery can be one of the most neuroprotective measures available; it establishes a slack brain for optimum operative conditions. Propofol also preserves cerebral autoregulation allowing compensation for reduced or increased MAP.[13] Propofol, however, like VGAs, reduces systemic vascular resistance. Decreases in systemic vascular resistance are particularly troublesome in hypovolemic bleeding patients seen in combat-related TBI. This effect is potentiated with propofol in hypovolemic patients.[34]

Ketamine was used for several reasons, including the perceived benefit of improved hemodynamic stability in this complex patient population. The addition of ketamine to a propofol TIVA can attenuate systemic hypotension because its sympathomimetic effects preserve MAP.[35–37] Historically, though, ketamine is thought to be contraindicated for neuroanesthesia because of adverse cerebral vascular and neurologic effects.[38,39] Ketamine is reported to increase ICP, increase cerebral blood volume and flow, be epileptogenic, and increase $CMRO_2$. Recent research disputes these long-held beliefs.[18,40] In older studies, ventilation was not controlled; ketamine actually decreases minute ventilation in spontaneous breathing nonintubated patients. This decrease in minute ventilation resulted in expected increases in $Paco_2$ and subsequent CBF increases, cerebral blood volume increases, and elevated ICP. When ventilation is controlled, however, ketamine, especially when combined with propofol or midazolam, tends to decrease ICP and $CMRO_2$ and not increase them.[19,41] Positron emission tomography scanning after ketamine administration demonstrates little change in $CMRO_2$ and only marginal increases in cerebral blood volume.[20] Regional oxygen extraction fraction decreases with ketamine alone.[20] Furthermore, ketamine possesses anticonvulsant properties in normocapnic patients at lower doses and does not seem to be epileptogenic as previously thought.[42,43]

Despite the favorable increases in SBP and improvements in hemodynamics associated with ketamine, subgroup analysis in our study demonstrates that ketamine was not associated with improved neurologic outcome. The low doses used in our study did not confer clinically significant differences in SBP compared with the VGA group. Conversely, ketamine was not associated with worsened neurologic outcome or mortality. At the doses used, we did not appreciate any psychomimetic phenomenon. Although the use of a propofol-based TIVA is supported by this study, the role of ketamine for neuroanesthesia remains unclear.

Beyond the hemodynamic and cerebral vascular effects, the potential role of anesthetics to effectively modulate or attenuate secondary brain injury in humans has received little attention, including at a recent National Institutes of Health workshop that comprehensively evaluated the evolution of prevention and treatment of secondary brain injury over the last few decades.[8] Recent research in TBI, however, targeting cellular interactions, offers more promising strategies to improve neurologic outcomes.[9,10] Examples of evolving areas of research include reduction in scavenging oxygen free radicals, prevention of excitotoxicity, maintenance of electrochemical ionic gradients, and inhibiting apoptotic mechanisms.[9,10] The unique contribution of anesthetic techniques to interact with these cellular targets is also evolving. Unfortunately, clinical studies documenting outcomes associated with differing anesthesia techniques are lacking.[11]

One of the proposed mechanisms of anesthetic techniques on cellular targets is modulation of the antiinflammatory and proinflammatory cascade.[30–32,44,45] In fact, propofol is associated with antioxidant effects, reducing oxygen free radicals and further cell injury as well as decreased infarct volume size in cerebral ischemia animal models.[17,31,32] Other potential mechanisms of propofol's action include γ-aminobutyric acid receptor inhibition and decreases in striatal dopamine accumulation after neuronal damage.[46] Finally, propofol prevents excitotoxic glutamate injury during neuronal ischemic events.[16]

Unique to our study is the population of combat-related neurotrauma. These patients present complex problems for the anesthesia provider choosing anesthetic drugs. Challenges include the presence of poly-

trauma in 30% of patients, severe hemorrhage, and long evacuation times.[6] Despite these challenges, mortality for patients requiring neurosurgical interventions for TBI has decreased from 19% during the Lebanon conflict, to 16% during Vietnam, to 11% during Operation Iraqi Freedom.[6,7,47,48] This mortality difference is likely multifactorial, including improved trauma care and improved neurosurgical techniques.[7,49]

The findings of decreased need for craniectomy and operative surgical time in the TIVA group could be confounded by time, neurosurgeon experience, or severity of injury, but they may also represent treatment effect. One hypothesis is that clinically relevant changes, such as less cerebral edema, may have resulted in these patients from TIVA, compared with those receiving VGA. Unfortunately, the neurosurgeons were not queried at the time of operation to support this contention.

There are important limitations in this study, especially the use of retrospective data. Unfortunately, the data and follow-up are limited because the data were obtained during active war. Temporal period, before and after August 21, 2004, was associated with indicators of injury severity and was confounded with treatment group (VGA, TIVA), rendering most treatment group contrasts potentially biased. Further, many other confounding factors, such as medical lessons learned resulting in improved processes and care over time, improvements in care and time during air evacuation, and increased rotations of medical providers, could not be controlled. However, there is a chance that differences between the VGA and TIVA groups did exist. Three of the 10 admission variables (heart rate, hematocrit, international normalized ratio) when stratified by group or date were statistically significant and demonstrated that the VGA patients may have presented to the CSH more severely injured. However, these three variables were likely not clinically significant, although we cannot exclude their importance. If patients were more severely injured in the VGA group, we would have expected to see more consistent differences in all of the admission variables in the stratified groups. Some other differences included a slightly higher incidence of bifrontal injury in the TIVA group *versus* the VGA group. Conversely, the admission GCS difference between groups was not statistically significant but was found to be independently associated with good or bad outcome. Moreover, Head Abbreviated Injury Score was not different between the VGA and TIVA groups. Therefore, the small difference in GCS between groups could impact outcomes in favor of TIVA. The effect of polytrauma in approximately 30% of our patients on neurologic outcome could also confound our analysis. As a result, we chose ISS, which is an assessment of total body injury over Abbreviated Injury Score to control for severity of injury. Several patients in both groups had surgeries for other injuries, and this was not evaluated in the analysis. Unfortunately, we were not able to obtain GOS determined 6 months after injury. In addition, logistical changes, rotations of anesthesia providers, individual provider preferences, access to records, and limitations imposed on research during military operations precluded the continued accrual of patients to improve the power needed to determine differences in anesthetic techniques.

The National Institutes of Health conference held in 2000 addressed study design issues in TBI and recommended a 6-month follow-up time point.[8] Experts also recommended the use of the extended GOS, which provides a better distinction between levels of disability and correlates well with several other outcome measurements after TBI, including neuropsychological and cognitive testing, disability rating score, and measures of perception of health (36-item Short-Form Health Survey).[50–53] Applying the extended GOS and application of detailed neurocognitive, behavioral, and psychological testing was not possible in the combat environment.

The numerical differences in mean hospital days, intensive care unit days, and ventilator days with regard to treatment temporal period are unfortunately difficult to interpret. These differences may be secondary to changing logistical constraints, casualty loads, and discharge practices at the CSH. For Americans air evacuated from Iraq to Germany and the continental United States, the effect of transport and changing levels of providers could not be controlled. In addition, while between-group differences in fluid resuscitation, blood product administration, and vasopressor use were not perceived as clinically significant, they could not be controlled for. These interventions could change the findings of this study.

While mortality is commonly a primary outcome in comparative studies, neurologic outcome is an equally acceptable outcome for TBI. As such, TIVA use did not reach statistical significance in multivariate analysis of mortality, but it is likely that this analysis was underpowered to detect such a difference. Combining mortality with neurologic outcome improved the power of our analysis. Moreover, these results may not be applicable to non–combat-related TBI. Finally, this study is hypothesis generating rather than conclusive. Based on our data, a prospectively planned study would require approximately 90 subjects per group to achieve a power of 80% to detect a benefit from TIVA relative to VGA with regard to good neurologic outcome equal to that presented in table 2, assuming two-sided testing with a significance level of 5%.

In conclusion, this study evaluating GOS at hospital discharge for combat-related TBI patients requiring operative neurosurgical intervention could not determine differences between propofol-based TIVA, often including ketamine, compared with VGA techniques. Confounding variables associated with injury severity and temporal periods significantly limited our ability to make definitive conclusions regarding the outcomes we stud-

ied. Unfortunately, the nature of combat research limited our ability to increase the numbers of patients studied or to prospectively randomize patients so we could appropriately power our study. Despite the retrospective design of this study and the concern that patients who received TIVA may have been less severely injured, this is the largest cohort of combat-related TBI patients reported to date. Given the potential widespread effects of the improvements in neurologic outcomes of this anesthetic strategy, we believe that further prospective evaluation is needed to determine whether outcome-related differences exist.

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Appendix: Glasgow Outcome Score[54]

Score	Description
1	Death
2	Persistent vegetative state Patient exhibits no obvious cortical function.
3	Severe disability Conscious but disabled. Patient depends on others for daily support.
4	Moderate disability Disabled but independent. Patient is independent as far as daily life. Disabilities include varying degrees of dysphasia, hemiparesis, or ataxia as well as intellectual and memory deficits and personality changes.
5	Good recovery Resumption of normal activities even though there may be minor neurologic or psychological deficits.

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