

# ANESTHESIOLOGY

## Etomidate *versus* Ketamine as Prehospital Induction Agent in Patients with Suspected Severe Traumatic Brain Injury

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### EDITOR'S PERSPECTIVE

#### What We Already Know about This Topic

- For patients with severe traumatic brain injury, there is debate as to which is the optimal induction drug for tracheal intubation in the prehospital setting
- Ketamine and etomidate are commonly used in this situation because they have better cardiovascular stability than barbiturates or propofol, but both ketamine and etomidate have potential adverse effects on intracranial pressure (ketamine) or adrenal suppression (etomidates)

#### What This Article Tells Us That Is New

- A retrospective analysis of a large database of patients with severe traumatic brain injury found no difference in mortality between the use of *S*(+)-ketamine and etomidate as induction agents for prehospital tracheal intubation

### ABSTRACT

**Background:** Severe traumatic brain injury is a leading cause of morbidity and mortality among young people around the world. Prehospital care focuses on the prevention and treatment of secondary brain injury and commonly includes tracheal intubation after induction of general anesthesia. The choice of induction agent in this setting is controversial. This study therefore investigated the association between the chosen induction medication etomidate *versus* *S*(+)-ketamine and the 30-day mortality in patients with severe traumatic brain injury who received prehospital airway management in the Netherlands.

**Methods:** This study is a retrospective analysis of the prospectively collected observational data of the Brain Injury: Prehospital Registry of Outcomes, Treatments and Epidemiology of Cerebral Trauma (BRAIN-PROTECT) cohort study. Patients with suspected severe traumatic brain injury who were transported to a participating trauma center and who received etomidate or *S*(+)-ketamine for prehospital induction of anesthesia for advanced airway management were included. Statistical analyses were performed with multivariable logistic regression and inverse probability of treatment weighting analysis.

**Results:** In total, 1,457 patients were eligible for analysis. No significant association between the administered induction medication and 30-day mortality was observed in unadjusted analyses (32.9% mortality for etomidate *versus* 33.8% mortality for *S*(+)-ketamine;  $P = 0.716$ ; odds ratio, 1.04; 95% CI, 0.83 to 1.32;  $P = 0.711$ ), as well as after adjustment for potential confounders (odds ratio, 1.08; 95% CI, 0.67 to 1.73;  $P = 0.765$ ; and risk difference 0.017; 95% CI,  $-0.051$  to 0.084;  $P = 0.686$ ). Likewise, in planned subgroup analyses for patients with confirmed traumatic brain injury and patients with isolated traumatic brain injury, no significant differences were found. Consistent results were found after multiple imputations of missing data.

**Conclusions:** The analysis found no evidence for an association between the use of etomidate or *S*(+)-ketamine as an anesthetic agent for intubation in patients with traumatic brain injury and mortality after 30 days in the prehospital setting, suggesting that the choice of induction agent may not influence the patient mortality rate in this population.

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Traumatic brain injury is one of the leading causes of morbidity and mortality among young people around the world.<sup>1–5</sup> Prehospital care for patients with severe traumatic brain injury focuses on the prevention and treatment of secondary brain injury and is considered a key factor in patient outcomes. In this context, prehospital endotracheal intubation and ventilation are commonly employed to prevent or treat airway obstruction, hypoxia, hypercapnia, and

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hypocapnia.<sup>6–9</sup> However, anesthesia is generally required before intubation to suppress airway reflexes, optimize intubation conditions, and avoid patient awareness of intubation. An ideal anesthetic induction agent for patients with traumatic brain injury would have minimal hemodynamic effects and limited side effects to preserve cerebral perfusion and oxygenation. In the prehospital setting, etomidate and ketamine—or, in recent years, its *S*(+) enantiomer—are commonly used.

Etomidate, a carboxylated derivative of imidazole, is a  $\gamma$ -aminobutyric acid receptor agonist. Etomidate is often considered a first-choice induction agent in critically ill patients<sup>10,11</sup> due to its relative hemodynamic stability, and it is also commonly used in patients with severe traumatic brain injury as it preserves cerebral perfusion pressure while decreasing intracranial pressure.<sup>12,13</sup> However, etomidate does not have analgesic properties and can cause adrenal suppression, which has been proven unfavorable in critically ill patients.<sup>14,15</sup>

Ketamine is an *N*-methyl-D-aspartate receptor antagonist.<sup>16</sup> It has sympathomimetic properties and causes less cardiovascular depression than other induction agents, preserves protective airway reflexes, and has a potent analgesic effect.<sup>15,17,18</sup> While these properties seem beneficial for patients with traumatic brain injury, the use of ketamine in this patient population remains controversial.<sup>19</sup> In the 1970s,

multiple studies found that ketamine causes an increase in intracranial pressure,<sup>20–23</sup> which may increase the risk of adverse outcomes in patients with traumatic brain injury. Although some more recent studies found no increases in intracranial pressure when ketamine is administered to patients with traumatic brain injury<sup>12,24,25</sup> and the neuroprotective effects of ketamine have been described,<sup>12,24,26</sup> a widespread concern regarding the use of ketamine in patients with traumatic brain injury persists.

At this time, it is unclear which induction agent should be preferred for the induction of prehospital anesthesia in patients with severe traumatic brain injury, and data regarding clinical outcomes are scarce. We therefore aim to investigate the association between the choice of anesthetic induction medication (etomidate *vs.* ketamine) and mortality in patients with severe traumatic brain injury who received prehospital anesthesia in the Netherlands.

## Materials and Methods

We conducted a retrospective analysis of the prospectively collected observational data of the BRAIN-PROTECT (**B**rain **I**njury: **P**rehospital **R**egistry of **O**utcomes, **T**reatments and **E**pidemiology of **C**erebral **T**rauma) study.<sup>2</sup> This multicenter observational cohort study focuses on prehospital treatment of patients with severe traumatic brain injury in the Netherlands. Patients with suspected severe traumatic brain injury (prehospital Glasgow Coma Scale of 8 or less and a trauma mechanism or clinical signs suggestive for traumatic brain injury) and who were treated by any one of the four Dutch helicopter emergency medical services were included in the BRAIN-PROTECT database. Suspicion of severe traumatic brain injury is a primary dispatch criterion for the helicopter emergency medical services in the Netherlands,<sup>27</sup> implicating that most severe traumatic brain injury cases are covered in the database. We deliberately based the inclusion on suspected severe traumatic brain injury rather than confirmed traumatic brain injury because prehospital treatment is based on the suspected rather than the definite diagnosis. It should be noted that in the Netherlands, steroids are not routinely administered to counteract the potential adrenal suppression effect of etomidate. Patients were included from February 2012 until December 2017, and follow-up data were collected until December 2018. A detailed protocol of this study has previously been published.<sup>2</sup>

For the current study, we selected patients from the BRAIN-PROTECT database who underwent prehospital advanced airway management requiring anesthesia and in whom either etomidate or *S*(+)-ketamine was used as induction agent. Patients were excluded from the analysis when they had been transported to a hospital other than one of the nine trauma centers participating in the BRAIN-PROTECT project (no follow-up data available) or if they had undergone traumatic cardiopulmonary resuscitation before hospital admission (such patients usually do

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not require anesthetic agents for airway management and inherently have a very high mortality irrespective of treatment). Patients were also excluded if they received both etomidate and *S(+)*-ketamine during prehospital treatment.

The collected data include demographic characteristics, medication use, American Society of Anesthesiologists classification, distance to hospital, vital signs before and after induction of anesthesia, Glasgow Coma Scale score, Injury Severity Score, and outcomes including survival. The primary outcome was 30-day mortality, and the secondary outcomes were systolic blood pressure after induction, Glasgow Outcome Scale score at discharge, length of hospital stay and length of intensive care unit (ICU) stay.

The Medical Research Ethics Boards of the Amsterdam University Medical Center, location Vrije Universiteit Medical Center and Erasmus Medical Center Rotterdam (The Netherlands) reviewed the study protocol and concluded that the research is not subject to the Dutch Medical Research Involving Human Subjects Act. The requirement for informed consent was waived. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.<sup>28</sup>

### Statistical Analysis

The previously published protocol of the BRAIN-PROTECT study includes a statistical analysis plan, as well as a power analysis.<sup>2</sup> The targeted sample size was 2,500 patients for the overall BRAIN-PROTECT database, and *a priori* calculations for analyses of subsets of the data set (as presented in this study) demonstrate that a sample size of 1,500 (close to the sample size in this study) has 80% power to detect a 6.4% difference in mortality.<sup>2</sup>

Stata 14.1 (StataCorp, USA) was used for the data analysis. The distribution of the data was assessed with histograms, Shapiro–Wilk tests and quantile–quantile plots. According to the distribution, means  $\pm$  SD or medians [25th, 75th percentile] are presented for continuous data or numbers and percentages for categorical data.

Unadjusted differences between the etomidate and *S(+)*-ketamine group were explored with a Mann–Whitney U test, *t* test, or chi-squared test. On the raw data, exploratory unadjusted analyses of the relationship between the induction medication and mortality were performed with logistic regression, as well as a Kaplan–Meier survival analysis and log-rank test.<sup>29</sup>

To account for potential confounders, we adjusted the logistic regression model for demographic variables (sex and age), preinjury health status (American Society of Anesthesiologists Physical Status), injury severity (injury severity score and first Glasgow Coma Scale), first measured prehospital vital parameters (systolic blood pressure, heart rate, and oxygen saturation) and operational characteristics (helicopter emergency medical service provider involved in treatment and distance to trauma center). In all these regression models, cluster robust standard errors were used to adjust

for nonindependence of patients treated within the same trauma centers. Planned subgroup analyses were performed for (1) patients with confirmed traumatic brain injury (head Abbreviated Injury Scale score of 3 or higher) and (2) isolated traumatic brain injury (head Abbreviated Injury Scale score of 3 or higher, scores for all other Abbreviated Injury Scales of 2 or lower). For the secondary outcomes, postinduction systolic blood pressure was analyzed with linear regression, the Glasgow Outcome Scale score at discharge was analyzed using ordinal logistic regression, and the length of hospital stay and length of ICU stay were analyzed using negative binomial regression.<sup>30</sup> The latter two outcomes were analyzed only for patients surviving to hospital discharge. All secondary outcomes were analyzed with and without adjustment for the potential confounders listed above. An additional *post hoc* sensitivity analysis was performed for the primary outcome using inverse probability of treatment weighting using propensity scores as a complementary approach to adjust for confounding.<sup>31,32</sup> Balance with respect to baseline variables was checked with standardized mean differences between the groups before and after weighting, and a standardized mean difference of less than 0.1 after weighting was considered an appropriate balance.<sup>33</sup>

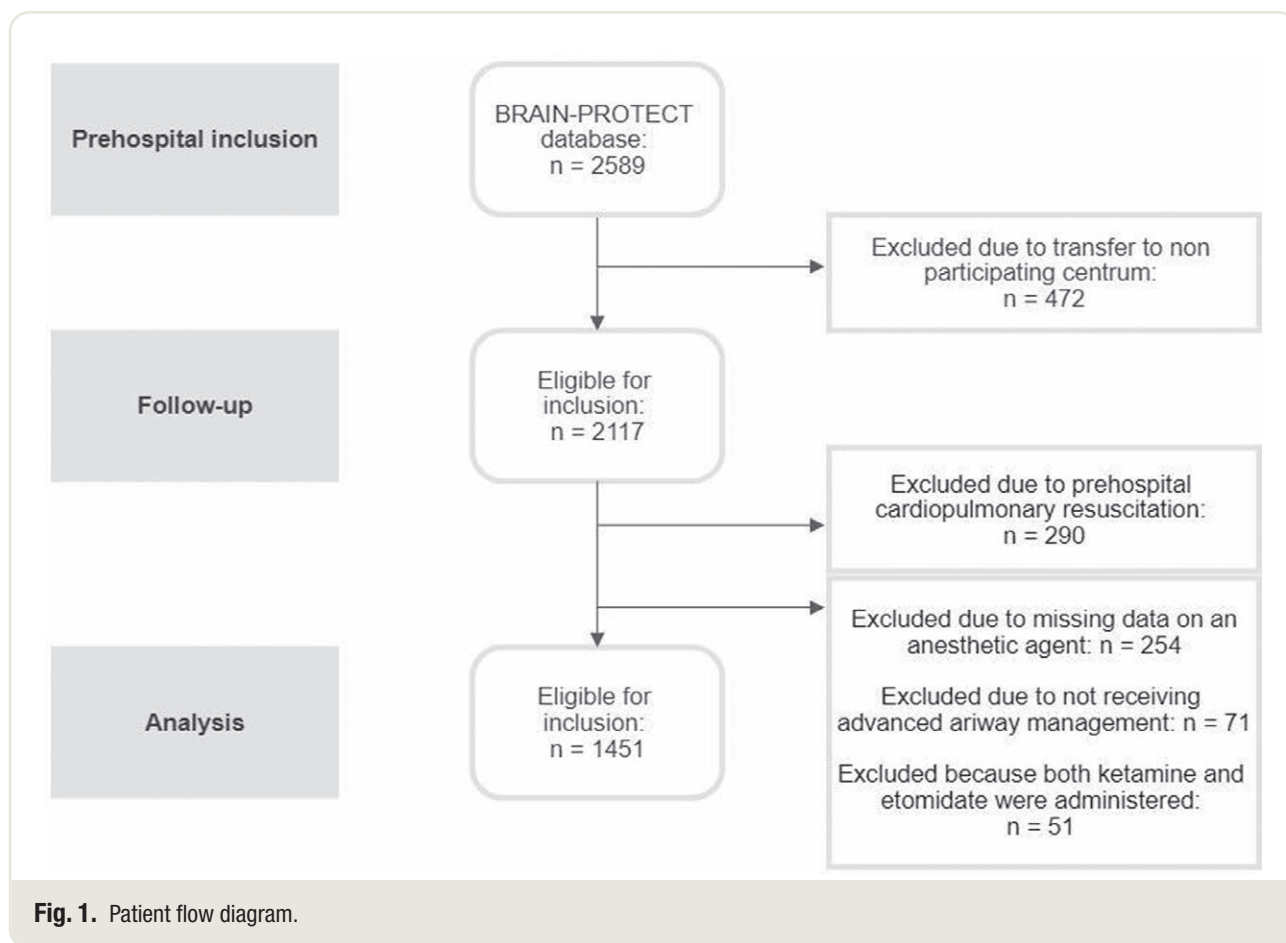
Analyses were primarily performed as complete-case analyses. Additionally, to gauge the potential effect of missing data on our conclusions, multiple imputation of 20 data sets was performed using chained equations, and coefficients and standard errors were adjusted for the variability across the imputed data sets according to Rubin's rules.<sup>34,35</sup>

### Results

In the BRAIN-PROTECT database, 2,589 patients are included. After removal of the data of patients transported to nonparticipating hospitals ( $n = 472$ ), patients undergoing prehospital cardiopulmonary resuscitation ( $n = 290$ ), patients not receiving advanced airway management and anesthesia ( $n = 71$ ), not receiving either etomidate or *S(+)*-ketamine ( $n = 254$ ), or receiving both etomidate and *S(+)*-ketamine ( $n = 51$ ), the data of a total of 1,451 patients were eligible for further analysis (fig. 1).

Of these patients, the majority were male (70.1%), the median age was 45 [24 to 65] years, and the median Glasgow Coma Scale at the arrival of a helicopter emergency medical services was 4 [3 to 7]; see table 1. A total of 955 patients (65.8%) received etomidate, and 496 patients received *S(+)*-ketamine (34.2%). Baseline characteristics were largely comparable between groups (table 1), but patients who received *S(+)*-ketamine had a higher heart rate (100 [80 to 120] *vs.* 90 beats per minute [71 to 110];  $P < 0.001$ ) at the arrival of a helicopter emergency medical service (*i.e.*, before induction of anesthesia).

After 30 days, the total mortality rate was 33.2%, with no significant difference between the groups in a direct, unadjusted comparison (etomidate, 32.9% and *S(+)*-ketamine, 33.8%;  $P = 0.716$ ; table 1), as well as in



unadjusted logistic regression (odds ratio, 1.04; 95% CI, 0.83 to 1.32;  $P = 0.711$ ) and in the Kaplan–Meier analysis with log-rank test ( $P = 0.324$ ; fig. 2). Similar results were observed after adjusting for potential confounders, with no significant association between the induction agent and odds of 30-day mortality in multivariable logistic regression (odds ratio, 1.08; 95% CI, 0.67 to 1.73;  $P = 0.765$ ; table 2). Likewise, inverse probability of treatment weighting analysis did not reveal a statistically significant or clinically relevant difference in the risk of mortality (risk difference, 0.017; 95% CI,  $-0.051$  to 0.084;  $P = 0.686$ ; see supplemental table in Supplemental Digital Content 1, <https://links.lww.com/ALN/D431>; baseline balance before and after inverse probability of treatment weighting). In a planned subgroup analysis, there was no statistically significant difference in survival at 30 days in patients with confirmed traumatic brain injury in multivariable logistic regression analysis (odds ratio, 1.07%; 95% CI, 0.65 to 1.76;  $P = 0.792$ ) and inverse probability of treatment weighting analysis (risk difference, 0.009; 95% CI,  $-0.064$  to 0.082;  $P = 0.809$ ). In addition, in the subgroup of patients with isolated traumatic brain injury, no difference was found in the confounder-adjusted logistic regression analysis (odds ratio, 0.82; 95% CI, 0.46 to 1.48;

$P = 0.520$ ) or in inverse probability of treatment weighting analysis (risk difference,  $-0.076$ ; 95% CI,  $-0.176$  to 0.024;  $P = 0.138$ ). Consistent results were found after multiple imputation (table 2).

We did observe a trend of increasing ketamine use and decreasing etomidate use over time. However, there was not a significant difference in mortality between etomidate and ketamine at any point in time. No association was observed between the induction medication and postinduction systolic blood pressure in unadjusted and confounder-adjusted analyses (unadjusted mean difference,  $-2.34$  mmHg; 95% CI,  $-6.76$  to 2.08;  $P = 0.257$ ; adjusted mean difference in linear regression,  $-1.29$  mmHg; 95% CI,  $-5.04$  to 2.46;  $P = 0.449$ ; adjusted mean difference after inverse probability of treatment weighting,  $-1.39$  mmHg; 95% CI,  $-5.74$  to 2.95;  $P = 0.529$ ). Similarly, there was no difference in Glasgow Outcome Scale scores at discharge between patients who received etomidate and those who received S(+)-ketamine as induction agent (unadjusted odds ratio, 0.88; 95% CI, 0.66 to 1.19;  $P = 0.418$ ; and adjusted odds ratio, 0.83; 95% CI, 0.60 to 1.16;  $P = 0.276$ ). The length of ICU stay also showed no significant difference (unadjusted incidence rate ratio, 0.97; 95% CI, 0.85 to 1.11;  $P = 0.639$ ; and adjusted incidence rate ratio,

**Table 1.** Patient Characteristics

Characteristics	Overall N (N = 1,451), (%)	Patients Who Received Etomidate (N = 955, 65.8%)	Patients Who Received Ketamine (N = 496, 34.2%)	P Value	Missing Data
Demographics and injury data					
Age	45 [24–65]	45 [24–65]	46 [23–65]	0.966	15
Male sex	1,015 (70.1)	664 (69.7)	351 (70.9)	0.627	3
Injury Severity Score	26 [20–35]	26 [20–35]	26 [20–35]	0.815	150
First Glasgow Coma Scale	4 [3–7]	4 [3–6]	4 [3–7]	0.201	0
Prehospital vital parameters at helicopter emergency medical services arrival					
Systolic blood pressure	140 [120–165]	140 [120–165]	140 [120–165]	0.360	199
Heart rate	94 [75–115]	90 [71–110]	100 [80–120]	< 0.001	78
Spo <sub>2</sub>	97 [93–99]	97 [93–99]	97 [93–99]	0.753	223
Vital parameters at emergency department arrival					
Systolic blood pressure	130 [110–150]	130 [110–150]	130 [110–147]	0.269	125
Heart rate	88 [75–105]	88 [74–105]	90 [77–106]	0.207	355
Spo <sub>2</sub>	100 [98–100]	100 [98–100]	100 [98–100]	0.642	236
Primary outcome					
Death at 30 days	456 (33.2)	296 (32.9)	160 (33.8)	0.716	77
Secondary outcome					
Length of stay in hospital in days	17.4 [2.0–24.0]	17.0 [2.0–23.0]	18.3 [3.0–26.0]	0.142	470
Length of stay in the intensive care unit in days	10.4 [2.0–14.0]	10.5 [2.0–14.0]	10.2 [2.0–14.0]	0.655	641
Glasgow Outcome Scale score at discharge					
Death	467 (35.2)	300 (34.7)	167 (36.1)	0.001	124
Vegetative state	34 (2.6)	21 (2.43)	13 (2.8)		
Severe disability	485 (36.6)	316 (36.6)	169 (36.5)		
Moderate disability	146 (11.1)	79 (9.1)	67 (14.5)		
Good recovery	195 (14.7)	148 (17.3)	47 (10.2)		

Spo<sub>2</sub>, oxygen saturation measured by pulse oximetry.

1.04; 95% CI, 0.91 to 1.18;  $P = 0.565$ ). Finally, the length of hospital stay exhibited no significant difference in the unadjusted analysis but was prolonged in patients receiving  $S(+)$ -ketamine after adjustment for potential confounders (unadjusted incidence rate ratio, 1.08; 95% CI, 0.95 to 1.22;  $P = 0.263$ ; and adjusted incidence rate ratio, 1.18; 95% CI, 1.05 to 1.32;  $P = 0.005$ ).

## Discussion

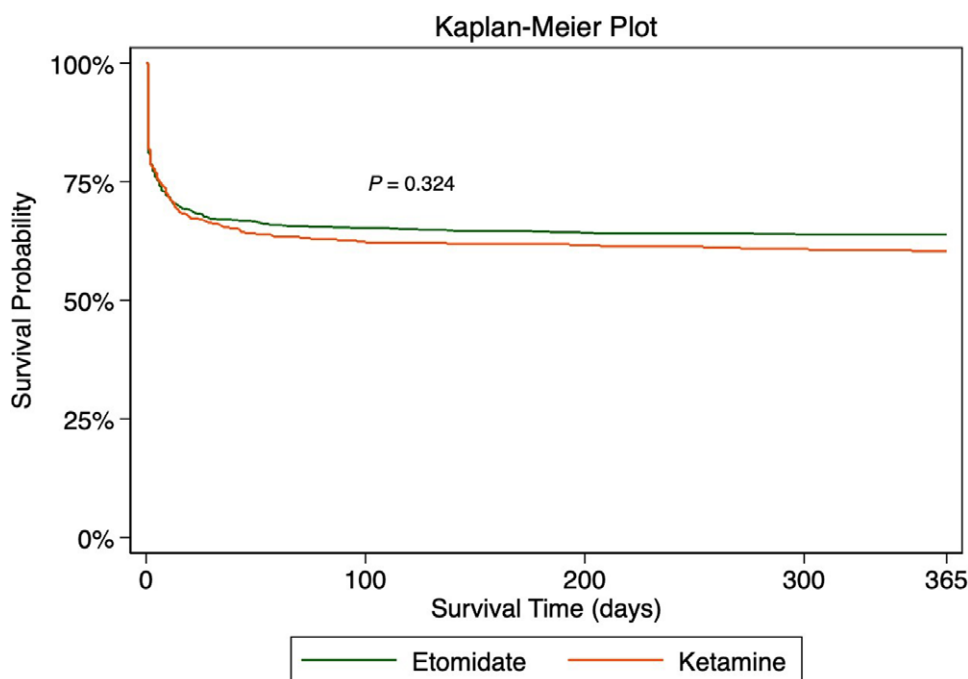
In this observational study, we investigated the association between two commonly used induction agents, etomidate and  $S(+)$ -ketamine, and mortality in patients with suspected severe traumatic brain injury who received prehospital anesthesia for advanced airway management. We found no evidence of differences in mortality after 30 days, in postinduction blood pressure, Glasgow Outcome Scale at discharge, or length of ICU stay. Only for the length of hospital stay, a statistically significant albeit rather small difference was found in favor of etomidate for patients who survived to hospital discharge.

Prehospital treatment of patients with suspected severe traumatic brain injury commonly involves securing the airway with an endotracheal tube to address or prevent airway obstruction and hypoxemia<sup>36,37</sup> and to allow for targeted ventilation.<sup>9</sup> However, laryngoscopy and tracheal intubation can trigger airway reflexes and activate the sympathetic

nervous system, potentially leading to complications such as laryngospasm, aspiration of gastric contents, arterial hypertension, and increased intracranial pressure.<sup>12</sup>

To mitigate these risks and ensure optimal intubation conditions, general anesthesia is necessary, even in unconscious patients. However, inducing general anesthesia can result in hemodynamic instability with arterial hypotension, a significant contributor to secondary brain injury and a predictor of unfavorable outcomes after traumatic brain injury.<sup>7</sup> Moreover, induction agents may have other unique pharmacologic properties that could be either beneficial or detrimental in specific patient groups, raising the question of which induction agent to prefer in patients with severe traumatic brain injury.

Etomidate and  $S(+)$ -ketamine are both considered relatively hemodynamically stable induction agents and are commonly used for prehospital emergency anesthesia in trauma patients.<sup>12</sup> A meta-analysis by Sharda *et al.*<sup>38</sup> reported a higher risk of postinduction hypotension in patients who received  $S(+)$ -ketamine, whereas other recent studies—*not included in that meta-analysis*—have failed to confirm this finding.<sup>39</sup> A possible explanation for this apparently controversial finding is that the effects of  $S(+)$ -ketamine on blood pressure may vary depending on patient characteristics. The hemodynamic stability after  $S(+)$ -ketamine administration is primarily mediated indirectly by sympathetic stimulation and catecholamine release, whereas  $S(+)$ -ketamine



**Fig. 2.** Kaplan–Meier plot of the estimated survival function (up to 1 yr after the trauma) per induction group: etomidate *versus* ketamine.

itself has direct negative inotropic effects.<sup>40</sup> Hence, S(+)-ketamine administration may plausibly lead to profound hemodynamic compromise in catecholamine-depleted critically ill patients,<sup>41</sup> whereas it may not lead to hemodynamic instability in patients with traumatic brain injury, who often tend to be quite healthy before the traumatic event.<sup>42</sup> Indeed, we did not observe lower blood pressures after S(+)-ketamine administration compared to etomidate in our study population. In fact, the data do not provide evidence for any statistically significant or clinically relevant differences in postinduction blood pressures, and both drugs appear to provide a similar degree of hemodynamic stability in the population of patients with suspected severe traumatic brain injury.

While maintaining hemodynamic stability is an important goal during induction of anesthesia in patients with severe traumatic brain injury, other characteristics of the induction drug need to be considered as well. Ketamine may have neuroprotective effects but has traditionally been considered contraindicated in traumatic brain injury.<sup>43</sup> Concerns about elevated intracranial pressure after ketamine administration persist despite a number of publications that found no evidence for increased intracranial pressures or decreases in cerebral blood flow.<sup>44–46</sup> Etomidate, on the other hand, causes transient adrenal dysfunction. Although there is still an ongoing debate about whether this adversely affects outcomes in septic patients,<sup>47</sup> data on the potential implications in patients with traumatic brain injury are completely lacking. Considering the known and

perhaps unknown advantages and drawbacks of both medications, it is unclear how benefits and harms balance each other out and what the relative net effect is of each drug on clinical outcomes.

We have neither directly measured intracranial pressures nor measured adrenal function or other surrogate outcomes but rather focused on the overall net effect of the drug on patient mortality as a clinically relevant endpoint. To our knowledge, only limited data are currently available regarding the effects of etomidate and ketamine for emergency intubation on mortality. This topic has been investigated in two randomized trials, in which, however, only a minority of participants were trauma patients. Matchett *et al.*<sup>48</sup> observed lower survival at 7 days in the etomidate group but no significant difference by day 28. Likewise, Jabre *et al.*<sup>15</sup> did not observe a difference in mortality risk during the 28-day follow-up period. In an observational study focusing on trauma patients and comparing outcomes before and after a switch from etomidate to ketamine as standard induction agent, Upchurch *et al.*<sup>49</sup> did not find significant differences in hospital mortality. Given the reported median Glasgow Coma Scale scores of 13 and 12, respectively, in the two treatment groups, it seems that most patients in that study did not have severe traumatic brain injury. To the best of our knowledge, our study is the first to specifically focus on the population of patients with severe traumatic brain injury. Consistent with the previous studies involving other patient populations, we did not find evidence for differences in mortality. Likewise, we found no evidence for an

**Table 2.** Association between the Induction Agent and 30-Day Mortality

Analysis	Odds Ratio	Risk Difference	CI	P Value
Logistic regression, complete case analysis				
All cases	1.08		0.67 to 1.73	0.765
Confirmed TBI	1.07		0.65 to 1.76	0.792
Isolated TBI	0.82		0.46 to 1.48	0.520
Inverse probability of treatment weighting analysis, complete case analysis				
All cases		0.017	−0.051 to 0.084	0.686
Confirmed TBI		0.009	−0.064 to 0.082	0.809
Isolated TBI		−0.076	−0.176 to 0.024	0.138
Logistic regression after multiple imputation				
All cases	1.081		0.783 to 1.493	0.637
Confirmed TBI	1.137		0.820 to 1.577	0.441
Isolated TBI	0.933		0.520 to 1.610	0.802
Inverse probability of treatment weighting analysis after multiple imputation				
All cases		0.011	−0.039 to 0.061	0.672
Confirmed TBI		0.018	−0.38 to 0.075	0.528
Isolated TBI		0.030	−0.108 to 0.049	0.457

Logistic regression analyses and inverse probability treatment weighting analyses on the association between the induction agent (etomidate *versus* ketamine, with etomidate being the reference category) and the primary outcome, mortality within 30 days. The logistic regression models, as well as inverse probability of treatment weighting, adjust for the following confounders: helicopter emergency medical service provider, physical status score preinjury, sex, age, first prehospital systolic blood pressure, first prehospital heart rate, first prehospital SpO<sub>2</sub>, first prehospital Glasgow Coma Scale, Injury Severity Score, and air distance to hospital.

ASA, American Society of Anesthesiologists; SpO<sub>2</sub>, oxygen saturation measured by pulse oximetry; TBI, traumatic brain injury.

association between the choice of induction drug and the secondary outcomes length of ICU stay, or functional outcome at discharge. It is plausible that other factors, such as the avoidance and treatment of factors associated with secondary brain injury (*e.g.*, prevention of hypoxia), as well as individual injury and patient characteristics, play more significant roles in determining patient outcomes than the choice of induction agent alone. Instead of rigidly adhering to a specific induction drug for all patients with traumatic brain injury, the choice of induction agent should be based on a comprehensive evaluation of multiple factors, including the patient's clinical condition, as well as physician preference.

The BRAIN-PROTECT study is a prospective observational project, and our current analysis of data from this database is subject to the inherent limitations associated with observational research. In the previously published study protocol, we detailed the steps that have been taken to minimize selection bias and information bias.<sup>2</sup> Incomplete data also cause an inherent limitation in observational data sets. However, analyses after multiple imputation<sup>34</sup> yielded results consistent with the complete case analyses, suggesting that the results are not significantly biased by missing data. Furthermore, confounding is an important source of bias in observational studies.<sup>50</sup> To address this concern, we have thoroughly adjusted for potential confounders using complementary statistical techniques, namely multivariable regression models, as well as propensity score–based inverse probability of treatment weighting. Both approaches yielded consistent

results. Nevertheless, residual confounding cannot be entirely ruled out, and we emphasize that while our data can be used to study associations, it cannot be used to establish causal relationships.

The data in our study were collected in the Netherlands, a country characterized by a high population density and a well developed emergency care infrastructure, with short distances to trauma centers. Consequently, the results may not be readily generalized to other healthcare systems. Moreover, it should be noted that in the Netherlands, the *S*(+) enantiomer of ketamine is used. *S*(+)-Ketamine has superseded racemic ketamine in clinical practice of anesthesia and emergency medicine in the European Union but has not yet been approved for intravenous use by the U.S. Food and Drug Administration. This enantiomer exhibits a higher affinity at the *N*-methyl-D-aspartate receptor binding site and an approximately four times higher anesthetic potency compared to the *R*(−) enantiomer.<sup>51</sup> Equianalgesic doses of the *S*(+) enantiomer and the racemate result in comparable increases in blood pressure and catecholamine concentrations.<sup>52</sup> Similarly, their effects on cerebral blood flow, cerebral blood volume, and cerebral metabolic rate of oxygen appear to be similar.<sup>53</sup> Our data do not allow direct conclusions on the effects of racemic ketamine *versus* etomidate on outcome. However, given the fact that racemic ketamine contains about 50% *S*(+)-ketamine, which is the pharmacologically more active component, and given the similar pharmacologic effects of the *S*(+) enantiomer and the racemate regarding hemodynamics and cerebral blood flow and metabolism,

there is no compelling reason to believe that the conclusions would differ when comparing racemic ketamine and etomidate. Another limitation is that the dose of the drugs was not standardized, which would not have been possible because dosing is based on patient weight, which, in turn, is usually unknown in the prehospital setting. Therefore, as is customary in prehospital clinical practice, choice of dose was at the discretion of the treating a helicopter emergency medical service physician.

In conclusion, our observational study found no significant difference in mortality, length of ICU, or functional status at discharge between patients with severe traumatic brain injury who received etomidate or *S(+)*-ketamine for prehospital induction of anesthesia. These results align with previous research in other patient populations. Further studies are warranted to explore potential associations with other important clinical endpoints, such as long-term functional outcomes.

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### Competing Interests

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### Supplemental Digital Content

Supplementary Table 1. Balancing baselines, <https://links.lww.com/ALN/D431>

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