Effect of Marijuana Use on Outcomes in Traumatic Brain Injury

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Traumatic brain injury (TBI) is associated with significant morbidity and mortality. Several studies have demonstrated neuroprotective effects of cannabinoids. The objective of this study was to establish a relationship between the presence of a positive toxicology screen for tetrahydrocannabinol (THC) and mortality after TBI. A 3-year retrospective review of registry data at a Level I center of patients sustaining TBI having a toxicology screen was performed. Pediatric patients (younger than 15 years) and patients with a suspected nonsurvivable injury were excluded. The THC(+) group was compared with the THC(–) group with respect to injury mechanism, severity, disposition, and mortality. Logistic regression was used to determine independent associations with mortality. There were 446 cases meeting all inclusion criteria. The incidence of a positive THC screen was 18.4 per cent (82). Overall mortality was 9.9 per cent (44); however, mortality in the THC(+) group (2.4% [two]) was significantly decreased compared with the THC(–) group (11.5% [42]; $P = 0.012$). After adjusting for differences between the study cohorts on logistic regression, a THC(+) screen was independently associated with survival after TBI (odds ratio, 0.224; 95% confidence interval, 0.051 to 0.991; $P = 0.049$). A positive THC screen is associated with decreased mortality in adult patients sustaining TBI.

IT IS ESTIMATED THAT in 2009, tetrahydrocannabinol (THC) use was a contributing factor in over 460,000 emergency department visits in the United States and it has also been linked to a higher incidence of motor vehicle crash involvement.[1, 2]

Animal models have shown cannabinoid analogs such as dexanabinol to be neuroprotective after trauma, demonstrating reduced glutamate excitotoxicity, free radical damage, and inflammatory response.[3, 4] Other animal studies have shown decreased vasospasm and inhibition of tumor necrosis factor-α, both of which are associated with neuroprotection.[5, 6]

Clinical investigations, however, have been limited. A Phase II study showed a decrease in intracranial pressure in patients given cannabinoid analogs, whereas a Phase III trial performed by the same group did not show any survival benefit.[7, 8] The impact of antecedent THC use on outcomes of trauma victims who survive to reach the hospital is not entirely understood.

The aim of this study is to establish a relationship between a THC positive screen and outcomes after TBI. Our hypothesis is that THC use may be associated with improved survival.

Methods

After Institutional Review Board approval, records of all trauma patients admitted to the surgical intensive care unit at Harbor-UCLA Medical Center from January 1, 2010, to December 31, 2012, were retrospectively reviewed. All patients sustaining traumatic brain injury (TBI) who had a urine toxicology screen performed were selected for the study. TBI was defined using the following *International Classification of Diseases, 9th Revision* codes: 800.1–800.39, 800.6–800.89, 801.1–801.39, 801.6–801.89, 803.1–803.39, 803.6–803.89, 804.1–804.29, and 804.6–804.79 (fractures with intracranial bleed); 851 (cerebral laceration and contusion, all), 852 (subarachnoid hemorrhage, subdural hemorrhage, extradural hematoma after injury, all), and 853 (other and unspecified intracerebral hemorrhage). Excluded from the study were pediatric patients (age younger than 15 years) and patients who either died, were made do not resuscitate, or had care withdrawn within the first 24 hours of admission.

Patient variables included age, gender, ethnicity, mechanism of injury, admission blood pressure, head Abbreviated Injury Score (Head AIS), and Injury Severity Score (ISS). Glasgow Coma Scale (GCS) was

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TABLE 1. *Comparison of Patients Meeting Demographic Inclusion Criteria with and without Toxicology Screen Results Documented (n = 538)*

Variable	Screen(+) (446 [82.9%])	Screen(–) (92 [17.1%])	*P* Value
Gender (male)	349 (78.3%)	67 (72.8%)	0.258
Mean age (years)	49.4 (±21.7)	43.7 (±20.5)	0.022
White *vs* nonwhite	149 (33.4%)	31 (33.7%)	0.958
Blunt *vs* penetrating mechanism	426 (95.5%)	88 (95.7%)	0.954
ISS ≥ 16	293 (65.7%)	57 (62.0%)	0.493

ISS, Injury Severity Score.

not included in our analysis because there was a significant number of patients who did not have this information recorded. However, Head AIS was deemed an accurate determination of severity of TBI. Outcome variables included survival, ventilator days, intensive care unit length of stay, hospital length of stay, disposition, and anticipated disability. Because not all patients who met demographic inclusion criteria had a toxicology screen available for review, we compared patients with and without a documented THC screen. Study patients were then classified according to THC screen results (THC[+] greater than 50 ng/mL).

The two study groups were compared using bivariate analysis. This was followed by logistic regression to determine independent associations with mortality. Results are expressed as means ± standard deviation, percentages, or raw data as indicated. Analysis was performed using χ^2 tests, Fisher's exact tests, or *t* tests where applicable, and *P* values < 0.05 were considered statistically significant. Continuous variables were dichotomized using clinically relevant cutpoints: age (45 years or older *vs* younger than 45 years), because this was close to the average age of our patient population; admission systolic blood pressure (less than 100 mmHg *vs* 100 mmHg or greater) and ISS (16 or greater *vs* less than 16) and Head AIS (4 or less *vs* greater than 4), because these values are commonly considered useful thresholds for injury severity in numerous previous studies. All statistical analysis was performed using SPSS software (Version 20 for Windows, Chicago, IL).

The following variables were used in the logistic regression model: THC(+), age 45 years or older, Head AIS four or greater, mechanism of injury, ethnicity, gender, alcohol greater than 0.08 per cent, and ISS 16 or greater. Adjusted odds ratios, 95 per cent confidence intervals, and *P* values were derived.

Results

In total, 7977 patients were evaluated by the trauma service during the study period and there were 4912 trauma activations. There were 538 patients who sustained TBI where 446 (82.9%) were screened for illicit drugs, constituting the study population. Patients with and without a toxicology screen documented are compared in Table 1. In the study group, 18.4 per cent (82) of patients tested positive for THC. Table 2 illustrates the demographics of the study group.

TABLE 2. *Demographics of Traumatic Brain Injury (TBI) Patients with Toxicology Screens Performed (n = 446)**

Variable	No. (%)/Mean ± Standard Deviation
THC	82 (18.4%)
Gender (male)	349 (78.3%)
Mean age (years)	49.4 (± 21.7)
Ethnicity	
Hispanic	139 (21.2%)
White	149 (33.4%)
Black	98 (22.0%)
Asian (other)	60 (13.5%)
Mechanism of injury	
Blunt assault	49 (11.0%)
Fall	219 (49.1%)
Motorcycle collision	17 (3.8%)
Motor vehicle collision	60 (13.5%)
Pedestrian/bicyclist *vs* MVC	81 (18.2%)
Gunshot wound	20 (4.5%)
ETOH (> 0.08%)	146 (32.7%)
Mean ISS	20.8 (± 10.9)
AIS Head ≥ 4	238 (53.4%)
Craniotomy	51 (11.4%)
Disposition	
Home without services	240 (53.8%)
Acute care facility	41 (9.2%)
Rehabilitation center	42 (9.4%)
Skilled nursing facility	32 (7.2%)
Disability	
Temporary handicap	328 (73.5%)
Permanent handicap	54 (12.1%)
Preinjury capacity	20 (4.5%)
Mortality	44 (9.9%)

* Exclusions: age ≤ 15 years, death ≤ 24 hours of admission, do-not-resuscitate status ≤ 24 hours of admission.

THC, tetrahydrocannabinol; MVC, motor vehicle crash; ETOH, alcohol; ISS, Injury Severity Score; AIS, Abbreviated Injury Score.

When compared with patients who were THC(–), THC(+) patients were more likely to be male (91.5 *vs* 75.3%, $P = 0.001$), were significantly younger (mean age 32.3 *vs* 53.2 years, $P < 0.001$), and were more likely to have also tested positive for alcohol (53.7 *vs* 28.0%, $P < 0.001$). There were also significant differences in race and injury mechanism; however, there was no significant difference in mean ISS

TABLE 3. *Comparison of THC(+) versus THC(–) in Patients with TBI (n = 446)*

Variable	THC(+) (82 [18.4%])	THC(–) (364 [81.6%])	*P* Value
Gender (male)	75 (91.5%)	274 (75.3%)	0.001
Mean age (years)	32.3 (± 13.8)	53.2 (± 21.3)	<0.001
Ethnicity			
Hispanic	26 (31.7%)	113 (31.0%)	<0.001
White	22 (26.8%)	127 (34.9%)	
Black	32 (39.0%)	66 (18.1%)	
Asian/other	2 (2.4%)	58 (15.9%)	
Mechanism of injury			
Blunt assault	9 (11.0%)	40 (11.0%)	<0.001
Fall	28 (34.1%)	191 (52.5%)	
Motorcycle collision	7 (8.5%)	10 (2.7%)	
Motor vehicle collision	15 (18.3%)	45 (12.4%)	
Pedestrian/bicyclist *vs* MVC	13 (15.9%)	68 (18.7%)	
Gunshot wound	10 (12.2%)	10 (2.7%)	
ETOH (> 0.08%)	44 (53.7%)	102 (28.0%)	<0.001
Mean ISS	22.3 (± 11.6)	20.4 (± 10.7)	0.160
AIS Head ≥ 4	48 (58.5%)	190 (52.2%)	0.299
Craniotomy	7 (8.5%)	44 (12.1%)	0.361
Disposition			
Home without services	53 (64.6%)	187 (51.4%)	0.024
Acute care facility	5 (6.1%)	36 (9.9%)	
Rehabilitation center	8 (9.8%)	34 (9.3%)	
Skilled nursing facility	3 (3.7%)	29 (8.0%)	
Disability			
Temporary handicap	69 (84.1%)	259 (71.2%)	0.042
Permanent handicap	9 (11.0%)	45 (12.4%)	
Preinjury capacity	2 (2.4%)	18 (4.9%)	
Mortality	2 (2.4%)	42 (11.5%)	0.012

THC, tetrahydrocannabinol; TBI, traumatic brain injury; MVC, motor vehicle crash; ETOH, alcohol; ISS, Injury Severity Score; AIS, Abbreviated Injury Score.

(22.3 *vs* 20.4, $P = 0.160$), Head AIS greater than four (58.5 *vs* 52.2%, $P = 0.299$), or need for craniotomy (8.5 *vs* 12.1%, $P = 0.361$). The THC(+) group had a significantly lower mortality rate than the THC(–) group (2.4 *vs* 11.5%, $P = 0.012$) (Table 3). Mortality was neurologically related in 100 per cent of THC(+) deaths (2 of 2) and 86 per cent of THC(–) deaths (36 of 42).

Using regression analysis to account for potential confounding variables (age, alcohol, AIS, ISS, mechanism of injury, gender, and ethnicity), a THC(+) screen was found to be an independent predictor of survival (odds ratio [OR], 0.224; 95% confidence interval [CI], 0.051 to 0.991; $P = 0.049$). Additionally, age 45 years or older and Head AIS greater than four were independent predictors of mortality (OR, 2.169; 95% CI, 1.001 to 4.399; $P = 0.050$ and OR, 10.922; 95% CI, 3.815 to 31.266; $P < 0.001$, respectively (Table 4).

TABLE 4. *Factors Independently Associated with Mortality after Traumatic Brain Injury**

Variable	Odds Ratio (95% CI)	*P* Value
Age ≥ 45 years	2.169 (1.001–4.399)	0.050
THC	0.224 (0.051–0.991)	0.049
AIS Head ≥ 4	10.922 (3.815–31.266)	<0.001

* Other variables entered: mechanism of injury, ethnicity, gender (male), ETOH (> 0.08%), ISS ≥ 16.

CI, confidence interval; THC, tetrahydrocannabinol; AIS, Abbreviated Injury Score; ETOH, alcohol; ISS, Injury Severity Score.

Discussion

The findings of our study are both pertinent and timely because recent legislation has been enacted to decriminalize the recreational use of THC. A number of studies has shown THC to be of medical benefit by increasing appetite, reducing ocular pressure, reducing muscle spasms, relieving pain, and alleviating symptoms associated with inflammatory bowel disease.[9–11] Given these potential advantageous properties, research had been directed to the study of potential neuroprotective effects of THC use.

As expected, our study showed that factors such as older age and higher Head AIS were independent predictors of mortality.[12] Our investigation suggests that a THC(+) screen is also an independent predictor of survival. This finding has support in previous literature because the neuroprotective effects of cannabinoids have been implicated in a variety of neurodegenerative diseases such as Alzheimer's disease, Huntington's disease, and multiple sclerosis.[13, 14] There is also data to support that cannabinoids provide a neuroprotective

effect in TBI. Dexanabinol (HU-211), a synthetic cannabinoid devoid of cannabimimetic effects, inhibits the production of tumor necrosis factor-α, a primary mediator of neurotoxicity after experimental TBI.[6]

In a Phase II clinical trial, patients treated with dexanabinol exhibited a reduction in the percentage of time with an intracranial pressure greater than 25, cerebral perfusion pressure less than 50, and systolic blood pressure less than 90 mmHg with a significant improvement in GCS at three months.[7] Despite this, a Phase III trial by the same investigators did not show a difference in mortality at six months; however, there was a significant decrease in mortality and a trend toward better outcomes in patients treated with dexanabinol at some study centers.[8]

A clinical series investigating the use of methamphetamines in patients sustaining TBI showed improved survival despite its known neurotoxic effects. However, this cohort of patients was more likely to have also tested positive for THC, and the authors implicated concomitant use of THC as a potential reason for improved outcomes.[15] Our study is the first to specifically associate THC use as an independent predictor of survival in TBI.

Comparing synthetic cannabinoids and THC in its native form is imperfect because these substances are not identical in composition. Timing of exposure may also play a role. In the Phase III trial described, dexanabinol was administered within six hours of arrival to the emergency department. This differs significantly from an uncontrolled study of a population of patients having used THC before injury who survive long enough to have had a toxicology screen performed. Perhaps earlier administration of naturally occurring compounds would yield different clinical results.

There are important limitations to this study. The retrospective nature of this analysis limits the conclusions that can be established and the study methodology was not able to ascertain any measure of acute *versus* chronic THC use. For standard urine toxicology screens (like the ones used in our study), detectable levels of THC can be present for an average of 4.6 days after last use for infrequent users to 15.4 days after last use for chronic users.[16] Therefore, the presence of a positive THC screen may not correlate with active intoxication or recent use. Furthermore, our study focused on survival outcomes despite differences in other discharge disability measures on bivariate analysis. Future investigations should look at functional neurologic outcomes more closely. Additionally, these results are based on patients with TBI having a urine THC screen performed. Because not all patients with TBI meeting initial inclusion criteria were tested for the presence of THC, this presents a level of bias that is unavoidable. However, an 82.9 per cent screen rate can be considered acceptable for any retrospective study and a comparison of patients screened and not screened shows reasonable similarities with the exception of age. Therefore, although our findings are applicable only to those who underwent toxicology screening, these have the potential to be applicable to those who did not have screen results documented. Finally, the THC(+) and (–) groups differed significantly demographically and by specific injury mechanism. However, it is pertinent that neither severity of overall injury (ISS) nor Head AIS differed between the study cohorts. In addition, we adjusted for these significant differences on logistic regression analysis.

Despite these limitations inherent to any retrospective study, our data suggest an important link between the presence of a positive THC screen and improved survival after TBI. With continued research, more information will be uncovered regarding the therapeutic potential of THC, and further therapeutic interventions may be established.

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