Recovery of Patients with Pure Diffuse Axonal Injury Who Remained in a Coma for 6 Hours or More

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BACKGROUND: **Diffuse axonal injury (DAI) is a traumatic brain injury and one of the most common causes of unfavorable outcome and death. The aim of this study was to investigate the recovery of patients with pure DAI who remained in a coma for 6 hours or longer after brain injury.**

METHODS: **This was a follow-up study of 75 patients diagnosed with pure DAI, aged 18–60 years, with a Glasgow Coma Scale score ≤8 at hospital admission. Patient data were collected at hospital admission, hospital discharge, and 3 and 6 months after DAI. Recovery was assessed by score changes in the Katz Index of Independence in Activities of Daily Living and Extended Glasgow Outcome Scale.**

RESULTS: **The percentage of patients in a coma for 6–24 hours, >24 hours without brainstem signs, and >24 hours with brainstem signs was 42.7%, 20%, and 37.3%, respectively. The 6-month mortality rate was 32.0%, and the mean Extended Glasgow Outcome Scale score among survivors decreased from 3.8 at discharge (SD = 1.2) to 2.1 at 3 months (SD = 1.6) and 1.2 at 6 months (SD = 1.6). The mean Katz Index of Independence in Activities of Daily Living scores were 8.5 (SD = 5.5), 3.5 (SD = 5.8), and 1.8 (SD = 4.5) at discharge and 3 and 6 months after trauma, respectively. Statistically significant differences were observed among the 3 evaluation periods.**

CONCLUSIONS: **Mortality was high among patients with DAI, but almost all survivors had favorable outcomes at 6 months. Functional improvement was more pronounced in the first 3 months.**

INTRODUCTION

Diffuse axonal injury (DAI) is characterized by microscopic lesions in long white matter tracts of the cerebral hemispheres, corpus callosum, and brainstem and is associated with significant mortality and morbidity. This traumatic brain injury (TBI) results from rotation of the brain and both gray and white matter displacement. The extent of DAI depends on the mechanism of trauma, occurring more frequently in cases of high-energy trauma, especially traffic accidents.[1-3]

DAI is considered the most important factor to predict morbidity and mortality in patients with TBI and is the most common cause of posttraumatic coma, disability, and persistent neurovegetative state.[1,2] Recovery after TBI is a dynamic, time-dependent, and relatively long process. Clinical studies have suggested that an improvement in the patient's condition occurs during the first year, in particular during the first 6 months.[4]

Few studies on DAI have investigated patient recovery after the injury. Among these, most are drug clinical trials and thus are of little use in elucidating evolution without pharmacologic intervention. Moreover, previous studies that analyzed recovery in patients with DAI reported different levels of functionality, even when evaluations were performed at similar time points after injury.[5-10] Differences in the characteristics of brain injury from the victims of these studies are probably related to the difficulty of

Key words
- Diffuse axonal injury
- Glasgow Outcome Scale
- Head trauma
- Recovery
- Severe traumatic brain injury

Abbreviations and Acronyms
AIS: Abbreviated Injury Scale
CT: Computed tomography
DAI: Diffuse axonal injury
GCS: Glasgow Coma Scale
GOS-E: Extended Glasgow Outcome Scale
ICU: Intensive care unit
ISS: Injury Severity Score
Katz ADL: Katz Index of Independence in Activities of Daily Living
TBI: Traumatic brain injury

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identifying their recovery pattern. Therefore, there are gaps in the knowledge of recovery in patients with DAI during the first 6 months after injury. Specifically, there are no functional studies of patients with pure DAI who remained in a coma for 6 hours or longer after brain injury. In this study, we analyzed functional recovery in a group of patients with DAI by assessing score changes in the Katz Index of Independence in Activities of Daily Living (Katz ADL) and Extended Glasgow Outcome Scale (GOS-E) at 3 periods: at hospital discharge and at 3 and 6 months after trauma.

This periodic assessment of functionality increases our understanding of how recovery proceeds after DAI. In clinical practice, it is important to have information on losses, deficiencies, and changes in the first 6 months after trauma to guide and evaluate the provided care. Indeed, understanding spontaneous improvement after injury helps fill gaps in our knowledge of the pathophysiologic process of brain recovery and may enable early identification of patients who do not evolve clinically. Moreover, knowing recovery patterns makes it possible to determine which resources are required to provide comprehensive care for patients and contributes to the development of systematized assistance for patient rehabilitation.[11-16]

MATERIALS AND METHODS

The present work was part of a follow-up study, with data collected at admission, hospital discharge, and 3 and 6 months after DAI. This study was approved by the Research Ethics Committee of the Nursing School and Medical School of the University of São Paulo. All participants freely consented to participation and signed the informed consent form. Written and informed consent was given by all participants or their legal representatives.

Participants

The present study included patients with pure DAI hospitalized at the study site from July 2013 to February 2014. Patients enrolled in this study had a Glasgow Coma Scale (GCS) score ≤8 at hospital admission and were aged 18–60 years.

The diagnosis of DAI was established on the basis of the following criteria: presence of indirect signs of DAI on computed tomography (CT), such as intraventricular hemorrhage, subarachnoid hemorrhage, gliding contusion, or diffuse swelling with effacement of the basal cisterns or grooves; signs of DAI on magnetic resonance imaging; or clinical evolution consistent with DAI and normal imaging findings.[17-23]

We excluded patients admitted to the hospital more than 6 hours after the traumatic event, patients transferred from other health services, patients previously diagnosed with TBI or with surgical TBI, patients with psychiatric disorders or chronic incapacitating pathology, patients who remained in a coma for less than 6 hours, and patients presenting with other intracranial lesions (Marshall CT classification ≥3)[24,25] and spinal cord lesions with a severity ≥3 according to the Abbreviated Injury Scale (AIS).[17]

Study Site

The present study was carried out at the University of São Paulo Medical School's Central Institute of the Clinics Hospital, a large hospital in the municipality of São Paulo, Brazil, that treats complex cases of trauma. Data collection was performed during hospital stay and at hospital discharge, and follow-up evaluations were performed at the neurosurgery outpatient center or at the patient's home if they were unable to travel during the evaluation period.

Measures

Information collected from patients included sociodemographic data, clinical variables related to the trauma, and indicators of trauma severity. The GOS-E[26-28] and Katz ADL[29] scales, instruments used to assess independence in performing activities of daily living, were used for the periodic evaluation of patient functionality.

The GCS score was recorded for all patients at admission, within the first 24 hours, and every day until discharge. In this study, coma was defined as the inability to open the eyes in response to painful stimuli or to obey commands.[17] The Injury Severity Score (ISS) was used to estimate trauma severity, and the coma duration (6–24 hours, >24 hours without brainstem signs [that is, decerebrate and decorticate posturing], and >24 hours with brainstem signs) was used to categorize the pure DAI.[17] After turning off the sedation, a score of 6 on the Best Motor Response item in the GCS was considered an indicator of recovery of consciousness.

To evaluate the global functionality of each patient, the GOS-E was applied with 7 categories: (0) upper good recovery, (1) lower good recovery, (2) upper moderate disability, (3) lower moderate disability, (4) upper severe disability, (5) lower severe disability, and (6) vegetative state.[26-28] The number of deaths due to pure DAI and complications in the 6 months after trauma also were recorded.

Functionality in activities of daily living was assessed by the Katz ADL, which measures independence in carrying out activities in 6 domains: bathing, dressing, toileting, transferring, continence, and feeding.[29] The score in each domain ranges from 0 to 3, and the total Katz ADL score ranges from 0 to 18. A lower score indicates greater independence to perform activities of daily living.[29]

Procedures

Hospitalized patients were monitored on a daily basis by the neurosurgery team using an electronic census that was updated continuously by the resident neurosurgery physicians at the hospital. Using this electronic census, we selected patients aged 18–60 years admitted in the previous 24 hours. After selection, patients were found in the emergency department, and their medical records were analyzed. We sought to select individuals admitted to the hospital up to 6 hours after trauma, with closed TBI, GCS ≤8 at admission, and indications of DAI in the imaging examination or a normal imaging examination.

After the lesions were diagnosed, we excluded patients who had other intracranial lesions (Marshall CT classification ≥3) or spinal cord lesions with AIS ≥3. We also excluded patients with chronic incapacitating pathology, psychiatric illness, or a previous diagnosis of TBI according to information provided by the patients or their relatives.

We collected sociodemographic, trauma-related, and clinical data from each patient during their hospital stay. After discharge, we administered the Katz ADL and GOS-E scales. In cases of discharge to home, patients and family members received guidance for outpatient follow-up 3 and 6 months after injury. Patients referred to other institutions who were still hospitalized at the study site or unable to travel were evaluated at home (1 patient at 3 months) or at the hospital (6 patients at 3 months). At 3 or 6 months after pure DAI, we assessed patient functionality using the Katz ADL and GOS-E scales.

Data Analyses

Data obtained in this study were stored in a computerized database and analyzed with Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, New York, USA) software, version 17.0. Descriptive statistics were performed for all variables to characterize the study sample. Categorical or ordinal variables were described with absolute and relative frequencies. Mean and standard deviation are presented for continuous and discrete numerical variables.

In the inferential analyses, we compared the results of the Katz ADL and GOS-E scales at discharge and 3 and 6 months after pure DAI to investigate patient recovery at each period. To compare the results among the 3 time points, the nonparametric Friedman test was used, as these were ordinal measures. Furthermore, this test was selected as it considers dependence between the results, and the evaluations were relative to those of the same patient. There was a significant difference between the results of the evaluations, and hence, multiple comparisons (the different periods were paired for each comparison) were made with the Student–Newman–Keuls test adapted for nonparametric tests.

To compare the mean of the total value of the Katz ADL among the 3 evaluation periods, we used the nonparametric Friedman test. If there was a statistically significant difference between periods, multiple comparisons (different periods were paired for each comparison) were made with the signed-rank Wilcoxon test with Holm–Bonferroni method. For all analyses, $P < 0.05$ was considered statistically significant.

RESULTS

Participants

Between July 2013 and February 2014, 143 patients with GCS score ≤8 were admitted to the hospital. Among this group, 78 patients met the inclusion criteria, and 65 were excluded because of the presence of psychiatric disorders (3 patients), presentation of other intracranial lesions and coma less than 6 hours (50 patients), a previous diagnosis of TBI (2 patients), spinal cord injury ≥3 AIS (3 patients), chronic disabling disease (2 patients), or transfer from another hospital (5 patients). Of the 78 patients originally included, 3 (3.8%) did not complete follow-up visits after hospital discharge. As such, a total of 75 patients who were followed-up until September 2014 were analyzed in the study. One patient in this group did not attend the 3-month evaluation but was still included in the analyses that did not concern this time point.

The majority (89.3%) of participants were men, with a mean age of 31.7 years (SD = 11.8) and 9.1 mean years of school (SD = 3.5). Most patients were of white ethnicity (65.3%), and the average family income per capita/per month was $578.27 (SD = $1,055.54; average price of the commercial dollar in the collection period [R$ 2.295,00]). The main cause of pure DAI was motor vehicle accident, with motorcyclists being the most frequent category (42.6%), followed by car occupants (26.7%).

Regarding trauma severity, the mean ISS was 35.6 (SD = 11.8). Individuals in a coma (GCS ≤8) at the moment of injury constituted 75.7% of trauma victims, with 79.5% of survey participants intubated at the scene of the incident. All patients had GCS score ≤8, as per the inclusion criterion. A GCS score of 3 was most common (57.3%), followed by GCS score 6–8 (30.7%) and GCS score 4–5 (12.0%). The percentage of patients in coma for 6–24 hours, >24 hours without brainstem signs, and >24 hours with brainstem signs was 42.7%, 20%, and 37.3%, respectively. The majority (70.7%) of patients had early signs of DAI on CT.

After hospital admission, 88.5% of patients were continuously sedated for an average of 4.1 days (SD = 4.3). The average time to achieve a score of 6 on the Best Motor Response item of GCS after sedation was turned off was 3.7 days (SD = 7.2).

Almost all patients (93.3%) were admitted to the intensive care unit (ICU), and the mean period of ICU stay was 11.7 days (SD = 15.5). During their ICU stay, only 3 (3.8%) patients required monitoring of cranial pressure (2 patient died). The mean hospital stay was 19.3 days (SD = 23.0).

Recovery Between Hospital Discharge and 6 Months Later

Of the 75 patients included in the study, 24 (32.0%) died in the first 6 months after trauma, all during hospitalization: 22 patients (91.6%) died during the first month after DAI, 1 (4.2%) died within 3 months, and another (4.2%) died before 6 months after the injury. Among those who died, mean GCS score was 3.8 (SD = 1.6), ISS was 44.4 (SD = 11.9), and survival time was 13.5 days (SD = 24.1). DAI deaths between the first 4 and 10 days were frequent (41.7%), and deaths occurring up to 3 days after the injury accounted for 29.1% of the total deaths that occurred in the first 6 months. Mortality among patients with coma >24 hours with brainstem signs was 78.6% and among the other victims of DAI, mortality was 6.3%.

The following tables and figures show the recovery data of the 51 survivors up to 6 months after trauma. Of the 51 patients who survived, 32 (62.7%) underwent treatment with specialists between discharge and 6 months after pure DAI. Physiotherapy was the most frequent treatment (49.0%), followed by occupational therapy (11.8%), psychological support (19.6%), and speech therapy (19.6%). At 6 months after DAI, 20 patients (39.2%) returned to work. However, of the patients who returned to work, one half (50.0%) changed the occupation.

Table 1 shows the frequencies of GOS-E categories at discharge and 3 and 6 months after trauma. The frequency of incapacitated individuals decreased significantly with time, whereas the number of patients with upper good recovery or lower good recovery increased. Nonparametric Friedman tests indicated a significant difference in GOS-E categorizations among the 3 evaluation periods ($P < 0.001$).

The recovery of patients with DAI according to mean GOS-E scores showed a trend of continuous clinical improvement, with the greatest progress observed in the first 3 months. Mean GOS-E scores improved from 3.8 (SD = 1.2) at discharge to 2.1 (SD = 1.6)

Table 1. Patients with DAI According to GOS-E Categories at Hospital Discharge and at 3 and 6 Months After Pure DAI

	Discharge		3 Months		6 Months	
GOS-E Categories	***n***	**%**	***n***	**%**	***n***	**%**
Upper good recovery	—	—	7	14.0	23	45.1
Lower good recovery	1	2.0	16	32.0	13	25.5
Upper moderate disability	8	15.7	10	20.0	5	9.8
Lower moderate disability	11	21.6	9	18.0	4	7.8
Upper severe disability	12	23.5	4	8.0	3	5.9
Lower severe disability	17	33.3	2	4.0	2	3.9
Vegetative state	2	3.9	2	4.0	1	2.0

$P < 0.001$, Friedman nonparametric test.
DAI, diffuse axonal injury; GOS-E, Extended Glasgow Outcome Scale.

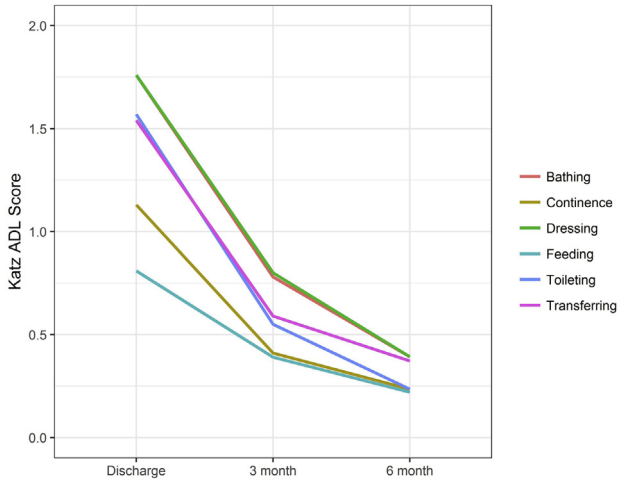

Figure 1. Mean scores on Katz Index of Independence in Activities of Daily Living (Katz ADL) scale items at hospital discharge and at 3 and 6 months after pure diffuse axonal injury.

at 3 months and 1.2 (SD = 1.6) at 6 months. All time-point comparisons returned statistically significant ($P < 0.001$) differences in GOS-E categorization.

Table 2 depicts Katz ADL scores at all 3 time points and a statistically significant difference among the evaluation periods ($P < 0.001$). It is possible to observe a decrease in the Katz ADL score over time, indicating patient improvement. Multiple comparisons with use of the Wilcoxon test with the Holm–Bonferroni method confirmed the difference between the mean Katz ADL scores for all evaluation periods ($P < 0.001$).

The mean scores of the 6 domains evaluated by the Katz ADL over time are shown in Figure 1. All mean scores decreased over time. We also observed statistically significant differences between discharge and 3 months and between discharge and 6 months, for all domains ($P < 0.001$). The items "transferring," "toileting," and "feeding" were not statistically significantly different between 3 and 6 months. However, for the other items, categorization was statistically significantly different between 3 and 6 months: "bathing" ($P = 0.018$), "dressing" ($P = 0.010$), and "continence" ($P = 0.037$).

Table 2. Descriptive Statistics and Comparison of Katz ADL Scores at Hospital Discharge and at 3 and 6 Months After Pure DAI

Katz ADL Scores	Mean (SD)	Median	Minimum	Maximum	*P**
Discharge	8.5 (5.5)	8.00	0	18	<0.001
3 months	3.5 (5.8)	0	0	18	
6 months	1.8 (4.5)	0	0	18	

Katz ADL, Katz Index of Independence in Activities of Daily Living; DAI, diffuse axonal injury; SD, standard deviation.
*Nonparametric Friedman test.

Tables 3 and 4 present study patients according to their recovery on the GOS-E (Table 3) and Katz ADL (Table 4) scales over time. For the GOS-E scale, no patient exhibited worsening functionality. Improvement between discharge and 6 months occurred in almost all cases (96.0%) (Table 3). Regarding the activities of daily living (Table 4), of the 51 patients available for the follow-up, 6 (11.8%) achieved the minimum score on the scale at hospital discharge and maintained during follow-up at 3 and 6 months, thus achieving total independence for activities of daily living. The majority (82.3%) of the remaining patients demonstrated functional improvement in activities of daily living between discharge and 6 months after trauma.

Six months after discharge, 88.2% of the surviving patients achieved GOS-E categorization consistent with independent

Table 3. Patients with DAI According to GOS-E After Trauma

	Period					
	Discharge to 3 Months		3–6 Months		Discharge to 6 Months	
GOS-E Recovery	***n***	**%**	***n***	**%**	***n***	**%**
Worsening	—	—	—	—	—	—
Unaltered	9	18.0	20	40.0	2	4.0
Improvement	41	82.0	30	60.0	49	96.0
Total	50*	100.0	50*	100.0	51	100.0

DAI, diffuse axonal injury; GOS-E, Extended Glasgow Outcome Scale.
*Excluding 1 patient who did not show up for the 3-month evaluation.

Table 4. Patients with DAI Who Did Not Achieve Maximum Katz ADL Scores After Hospital Discharge

Katz ADL Scores Evolution	Period					
	Discharge to 3 Months		3–6 Months		Discharge to 6 Months	
	n	%	*n*	%	*n*	%
Worse	1	2.0	1	2.0	2	4.0
Unaltered	9	18.0	32	64.0	7	13.7
Improved	40	80.0	17	34.0	42	82.3
Total	50*	100.0	50*	100.0	51	100.0

DAI, diffuse axonal injury; Katz ADL, Katz Index of Independence in Activities of Daily Living.
*Excluding 1 patient evaluated in the 3-month period.

living, and 45.1% were classified as upper good recovery (Table 1). The vast majority of patients had complete independence in daily life activities, ranging from 80.4% to 90.2% in the 6 domains of the Katz ADL. Considering all the scale's domains, 86.3% had signs of independence in the activities evaluated by the scale (i.e., they did not require assistance).

Of the 6 survivors in a coma >24 hours with brainstem signs, 5 (83.3%) were dependent at the end of the follow-up period. Among the other 45 patients, only 1 (2.2%) was still dependent.

DISCUSSION

DAI is a specific type of injury that occurs in patients with TBI and is associated with significant mortality and morbidity. The results of this study confirm the high rate of mortality among patients with pure DAI who remained in a coma for 6 hours or more after brain injury. The number of deaths observed up to 6 months after trauma was significant (32.0%); this was similar to some previous reports[7,30,31] and greater than that observed in other studies.[9,10,32] This difference may be related to the period in which deaths were recorded (up to 2 years) and the eligibility criteria applied, as well as trauma and DAI severity. In this study, mortality was much greater among patients with coma >24 hours with brainstem signs (78.6%), and among the other patients with DAI, mortality was 6.3%.

The evolution of recovery of patients with pure DAI during the first 6 months after trauma was the central focus of this study, considering indications from the literature that this period is characterized by most functional recovery gains.[11] The statistical results of the current study corroborate these indications; over time, patients achieved a significant improvement in functional capacity according to the GOS-E scale. Between hospital discharge and 6 months after pure DAI, analysis of recovery showed improvements in functional capacity on the GOS-E and Katz ADL scales in 96.0% and 82.3% of cases, respectively.

A study that analyzed patient recovery over a similar time period revealed favorable outcomes (upper good recovery, lower good recovery, or moderate disability) in 40.3%, 79.6%, and 97.8% of patients at discharge and 3 and 6 months after trauma, respectively.[9] These frequencies are similar to those obtained in this study when a similar grouping of GOS-E categories was performed (39.3%, 84.0%, and 88.2%, respectively). Both sets of results showed that the frequency of individuals with unfavorable results (persistent vegetative state, severe disability) decreased with time, especially in the first 3 months, whereas the frequency of those with favorable results increased.

Performing later and sparse evaluations, other studies revealed significant improvement in patients with DAI up to 2 years posttrauma, suggesting that 6 months may not be sufficient to achieve stable recovery after DAI.[10] However, we must consider the possibility that late measures are influenced by other events after trauma and, especially, by the adaptation of patients to their incapacities.[33,34]

There were decreases in the mean Katz ADL score for all periods. Differences in these values indicated statistically significant improvements in daily life activities between the 3 evaluation periods. However, the differences between the 3 evaluations were evident in the domains of bathing, dressing, and toileting. As for transferring, continence, and feeding, recovery occurred in the first 3 months after pure DAI, the capacity for transferring and feeding tended to stabilize with minimum score on the scale in the subsequent period. Moreover, considering the values obtained for the Katz ADL and GOS-E scales, functional improvement was more pronounced in the first 3 months, although it continued to occur up to 6 months after pure DAI.

By 6 months after pure DAI, 88.2% of the survivors achieved GOS-E categorization with independent living, whereas 45.1% demonstrated complete trauma recovery. In this period, 29.4% of individuals had disabilities, and of these, 11.8% were dependent. In daily life activities, the majority of patients were completely independent at 6 months, with a frequency ranging from 80.4% to 90.2% in the 6 domains of the Katz ADL. Considering all domains, 86.3% patients showed independence in the evaluated activities.

A study that used the Barthel Index to assess the ability of patients with DAI to perform daily life activities reported a mean score of 80.7 at 6 months, indicating independence in these activities.[35] Previous groups[36,37] that assessed daily life activities in patients with TBI reported frequencies of independent patients at 6 months posttrauma that were lower than those described here. Patients with severe TBI only achieved this level of improvement 2–5 years after trauma.[33,38,39]

Overall, patients with pure DAI were independent according to both GOS-E (88.2%) and Katz ADL (83.3%) at 6 months. The literature describes worse outcomes for patients with DAI in this period.[5-7] However, the majority of the participants in this study remained in a coma for 6–24 hours (42.7%) or >24 hours without brainstem signs (20.0%); of these patients, only 2 died, and 1 (2.2%) remained dependent after 6 months. It is notable that functional improvement was more pronounced in the first

3 months in both groups and that almost all patients with brainstem signs died or were dependent at 6 months.

Study Strengths and Limitations

Some limitations should be considered alongside our findings. The study sample included patients from a single institution, a referral center for high-complexity cases, and not all participants were enrolled in rehabilitation services during the follow-up period. However, all patients who remained dependent at 6 months posttrauma were assisted in their recovery by specialists. The lack of magnetic resonance imaging data in a subset of the study participants can also be considered a limitation, because such images would have allowed the comparison between patients' clinical recovery and specific brain lesions.

CONCLUSIONS

Mortality was high among patients with DAI, especially among those who remained in a coma >24 hours with brainstem signs. However, almost all survivors had favorable outcomes at 6 months after trauma. Functional improvement was more pronounced in the first 3 months. The findings of our study will aid in understanding the recovery of patients with important pure DAI and contribute to formulating strategies for social reintegration of patients with this injury.

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