

ORIGINAL RESEARCH

Computed tomography for patients with drug- or substance-induced seizures: a retrospective analysis

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Abstract

Introduction: Seizure is a common poisoning-related neurological presentation in the emergency department (ED). Although brain computed tomography (CT) is recommended in patients presenting with first seizures, its role in patients with a suspected drug/substance-induced seizure (DSS) remains inconclusive. This study evaluated whether brain CT examination changes the management and outcome of DSS patients.

Methods: We retrospectively reviewed adult patients presenting to the ED with a DSS in Linkou and Taipei Chang Gung Memorial Hospital, Taiwan, from January 2008 to December 2015. We also analyzed whether the brain CT examinations found meaningful acute abnormalities and their impact on subsequent management. We compared the differences between DSS patients undergoing CT scans or not to identify factors that affect the decision to arrange brain CT.

Results: The study enrolled 97 patients (69 males). The most common cause of DSS was alcohol withdrawal (58.76%), followed by carbon monoxide (12.37%) and stimulants (8.25%). Eight (8.25%) patients developed status epilepticus, 15 (15.46%) were intubated, and 37 (37.76%) were admitted, including 12 (12.26%) to the intensive care unit. Brain CT was performed in 64 (66.0%) patients and four had abnormal reports that led to further imaging studies. The abnormal findings ultimately had no significant clinical impact. Patients who underwent CT scans had a worse Glasgow Coma Scale score ($p = 0.024$) and higher rate of status epilepticus ($p = 0.031$).

Conclusion: Brain CT does not provide substantial information for the care of DSS patients. Multi-center prospective studies are needed to obtain stronger evidence.

Keywords

Seizure; Poisoning; Computed tomography; Anticonvulsants; Alcohol withdrawal

1. Introduction

Overdose and substance poisoning are major health issues globally. The World Health Organization estimated that 193,460 people died worldwide from unintentional poisoning in 2012 and nearly a million people die each year as a result of suicide [1]. Drug or substance poisoning can damage various organs. Seizure is a common poisoning-related neurological presentation in the emergency department (ED) [2]. An estimated 6% of new-onset seizures and up to 9% of status epilepticus cases are due to overdose or poisoning [3, 4].

Most drug/substance-induced seizures (DSSs) occur as a result of changes in the balance of excitatory and inhibitory neuronal activity, transmitters, and pathways, leading to involuntary discharge of the cerebral cortex [5]. The majority of DSSs manifest as generalized tonic-clonic seizures (GTCSs). Although most DSSs are not caused by actual brain damage, some studies have shown that poisoning might result in local

brain injury and trigger seizures [6, 7].

Brain computed tomography (CT) is frequently used to evaluate intracranial lesions in patients with altered mental status or seizures in the ED. A high proportion of overdose and poisoned patients undergo brain CT [2, 8] and seizure is a common indication for CT examinations. CT is used widely because of its accessibility and reliability, but performing CT can be risky because it requires critically ill patients to leave closely monitored areas temporarily. Radiation exposure and the high cost are also of concern. Although brain CT in patients with a first GTCS is generally accepted [9–12], it is not clear whether a patient with a DSS requires brain CT.

This study explored whether brain CT has a significant impact on the management and outcome in patients with DSS.

2. Materials & methods

TABLE 1. Demographic and clinical data of DSS patients and the comparison between group A and group B.

Characteristic	All	Group A (brain CT performed)	Group B (brain CT not performed)	p value (between group A and B)
No. of patients	97	64	33	
Age (years)	40.36 ± 12.95	39.38 ± 11.25	42.27 ± 15.76	0.35
Sex (M), n (%)	69 (71.13)	46 (71.88)	23 (69.7)	1
Single seizure, n (%)	69 (71.13)	41 (64.06)	28 (84.85)	0.06
Status epilepticus, n (%)	8 (8.25)	8 (12.5)	0 (0)	0.031
BT (°C)	36.91 ± 1.21	36.97 ± 1.35	36.81 ± 0.89	0.49
PR (beats/min)	108.59 ± 23.42	109.83 ± 23.37	106.18 ± 23.68	0.47
RR (breaths/min)	19.74 ± 2.61	19.95 ± 2.64	19.33 ± 2.55	0.27
SBP (mmHg)	137.64 ± 31.25	137.17 ± 32.33	138.55 ± 29.49	0.84
DBP (mmHg)	85.96 ± 23.64	86.59 ± 24.05	84.73 ± 23.14	0.71
GCS	12.81 ± 3.77	12.27 ± 4.12	13.88 ± 2.74	0.024
WBC (cells/μL)	10554.35 ± 5812.10	10496.7 ± 5406.6	10667.74 ± 6632.16	0.89
Creatinine (mg/dL)	1.04 ± 0.75	1.11 ± 0.88	0.91 ± 0.37	0.13
ALT (U/L)	55.82 ± 67.89	57.13 ± 77.18	53.21 ± 45	0.77
Na (meq/L)	137.79 ± 10.56	137.28 ± 12.58	138.86 ± 3.68	0.37
K (meq/L)	3.49 ± 0.66	3.51 ± 0.71	3.45 ± 0.55	0.67
Ca (mg/dL)	8.6 ± 0.8	8.63 ± 0.85	8.51 ± 0.66	0.73
pH	7.34 ± 0.15	7.31 ± 0.17	7.38 ± 0.08	0.07
PCO ₂ (mmHg)	37.54 ± 9.71	39.32 ± 10.33	34.88 ± 8.23	0.11
HCO ₃ (mmol/L)	20.08 ± 5.81	20.29 ± 6.74	19.78 ± 4.19	0.74
Lactate (mg/dL)	40.85 ± 32.78	38.52 ± 17.01	44.73 ± 56.09	0.82
Intubation, n (%)	15 (15.46)	13 (20.31)	2 (6.06)	0.12
Admission, n (%)	37 (38.14)	25 (39.06)	12 (36.36)	0.97
Admission LOS (day)	14.86 ± 15.96	18.04 ± 17.72	8.25 ± 8.84	0.032
ICU, n (%)	12 (12.37)	10 (15.63)	2 (6.06)	0.15
ICU LOS (day)	10.58 ± 8.05	11.50 ± 8.46	6.00 ± 4.24	0.40
Survive (survive/death)	94/3	61/3	33/0	1

Continuous data are shown as mean ± SD. Abbreviations: CT, computed tomography; BT, body temperature; PR, pulse rate; RR, respiratory rate; SBP/DBP, systolic/diastolic blood pressure; GCS, Glasgow coma scale; ICU, intensive care unit; LOS, length of stay.

2.1 Study design and settings

This retrospective chart-review study enrolled adult ED patients in Linkou Chang Gung Memorial Hospital (annual ED visits around 180,000) and Taipei Chang Gung Memorial Hospital (annual ED visits around 50,000) who presented between January 2008 and December 2015 with a GTCS that was suspected as being due to drug overdose, substance poisoning, or substance withdrawal. This study was approved by Chang Gung Institutional Research Board (IRB: 20160883B0).

2.2 Study protocols

2.2.1 Patient identification, inclusion and exclusion

We recruited candidates by searching the electronic medical records using the following criteria: (1) poisoning- or overdose-related ICD-9 codes; (2) free text search with the

key words “seizure”, “convulsion”, “generalized tonic clonic seizure”, “GTC”, and “status epilepticus”; and (3) age >18 years.

A medical toxicologist reviewed the records of all candidates. The study included patients who presented with a single or multiple GTCSs considered due to poisoning, overdose, or substance withdrawal by the physician in charge. Patients with the following conditions were excluded: younger than 18 years old, pregnancy, uncertain drug/substance exposure history, concomitant head trauma, history of epilepsy, or incomplete medical records. We also excluded patients who presented with focal neurological deficits or focal seizures, since they would undoubtedly need brain imaging.

2.2.2 Data acquisition

Once included, the research team collected each patient’s age, sex, culprit drug/substance of seizure, exposure history, time of

ingestion, initial vital signs, initial Glasgow coma scale (GCS) score, symptoms, seizure pattern (single seizure, multiple, or status epilepticus), laboratory data, hospital flow, severity of toxicity (recorded as the Poison Severity Index) [13], poisoning-related therapy, admission period, and outcome for descriptive analysis. Brain CT reports were reviewed and all pathological imaging findings were recorded, as well as reports of consequential brain magnetic resonance imaging (MRI) or angiography examination. The culprit drugs/substances were determined by the medical toxicologist. Status epilepticus was defined as a continuous seizure lasting for 5 or more minutes, or repetitive seizures without regaining consciousness.

2.3 Study outcomes

Patients who underwent brain CT were assigned to group A and those who did not were assigned to Group B. We then analyzed whether the brain CT examinations of Group A found any meaningful results and their impacts on the subsequent management. We also analyzed the differences in the clinical characteristics of groups A and B to identify the factors that affected the decision to arrange brain CT for patients with DSSs. The anticonvulsants used to treat the seizures and their efficacy were also recorded and analyzed.

2.4 Statistical analysis

The Mann-Whitney U-test was used to compare continuous variables between the groups, and the chi-square or Fisher's exact test was used to compare categorical variables between groups, as appropriate. A p -value < 0.05 was considered statistically significant. To evaluate the treatment efficacy, the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All analyses were performed using SAS Enterprise Guide 9.4.

3. Results

The study included 97 patients who met our criteria. The average age was 40.36 ± 12.95 years and 69 (71.13%) were males. Table 1 summarizes their demographic information and Table 2 lists the culprit drugs/substances. The most common cause of DSSs was alcohol withdrawal, accounting for more than half of the patients (57 patients, 58.76%), followed by carbon monoxide (12 patients, 12.37%), and stimulants (8 patients, 8.25%). While 69 patients (71.13%) had only a single GTCS, eight (8.25%) had status epilepticus. Fifteen (15.46%) patients required endotracheal intubation. Of the patients, 37 (37.76%) were admitted to an ordinary ward and 12 (12.26%) to the intensive care unit. Three patients ultimately died: two from the poisoning and the third from an underlying disease.

The 64 patients who underwent brain CT were assigned to Group A. All CT examinations were completed within 6 hours of hospital arrival. The 33 patients who did not undergo CT were assigned to group B. In Group A, four (6.25%) patients had an abnormal CT report (Table 3). CT images with the key findings of these four patients are shown in Fig. 1. The CT reports of patients one and two showed possible brain infarction and that of patient three was suspicious of both cerebral infarction and cerebral aneurysm. Patient one did not

TABLE 2. Substances that caused seizures in the enrolled patients.

Substances	n (%)
Total DSS case	97
Alcohol withdrawal	57 (58.76%)
Carbon monoxide	12 (12.37%)
Stimulants	8 (8.25%)
Pesticides	4 (4.12%)
Antidepressants	3 (3.09%)
Flumazenil	2 (2.06%)
Heroin withdrawal	2 (1.03%)
Alcohol (massive)	1 (1.03%)
Camphor	1 (1.03%)
Diphenhydramine	1 (1.03%)
Ketamine	1 (1.03%)
Methanol	1 (1.03%)
Tramadol	1 (1.03%)
Zolpidem withdrawal	1 (1.03%)
Multiple drugs	1 (1.03%)
Unknown substance	1 (1.03%)

have any neurological symptoms and no further imaging study was arranged. Patients two and three underwent subsequent brain MRI or brain angiography and the results were negative for any acute abnormality. Patient four, who had a CT report of brain edema and increased intracranial pressure, was treated supportively with intravenous lorazepam, antiemetics, and hypertonic saline infusion (for hyponatremia). She did not receive any intracranial pressure-lowering therapies.

Table 1 compares Groups A and B. Group A had worse GCS scores on arrival ($p = 0.024$) and higher rates of status epilepticus ($p = 0.031$). Groups A and B had similar admission rates, but once admitted, Group A had longer hospital stays ($p = 0.032$).

Approximately half of the patients (46) had a single GTCS either before ED arrival or in the ED and were not treated with any anticonvulsant; the other 51 cases were treated with anticonvulsants, and benzodiazepines were the most common first-line therapy (Table 4). Initially, 25 cases were treated with diazepam and 14 of them had repeat seizures that required re-dosing or other anticonvulsants. Lorazepam was given to 17 patients initially, and 6 had a repeat seizure. While patients initially treated with lorazepam had a lower rate of seizure recurrence, the treatment efficacies of the two drugs did not differ significantly (OR 2.33, 95% CI 0.65–8.30). The clinical parameters and disease severity of the patients initially treated with diazepam or with lorazepam did not differ, except the valium group was older (45.72 ± 15.63 vs. 35.94 ± 9.00 years, $p = 0.014$). Four patients were initially treated with midazolam; three of them had status epilepticus and received continuous midazolam infusions. Five patients were initially treated with a non-benzodiazepine antiepileptic; none had a witnessed GTCS on ED arrival. Because of the small

TABLE 3. Clinical presentations, subsequent tests, and outcomes of patients with abnormal brain CT reports.

Patient	Age/Sex	Clinical presentation	Brain CT findings	Subsequent tests & treatment	Outcomes
1	52/M	alcoholism, GTCS	suspect cerebellum infarction	non	discharge without sequela
2	55/F	alcoholism, GTCS	suspect small infarction	MRI: no infarction	discharge without sequela
3	56/M	alcoholism, GTCS	suspect lacunar infarction and possible aneurysm	MRI & angiography: both normal	discharge without sequela
4	32/F	GTCS after stimulant use	brain edema, IICP	non	discharge without sequela

Abbreviations: GTCS, generalized tonic-clonic seizure; IICP, increased intracranial pressure; MRI, magnetic resonance imaging.

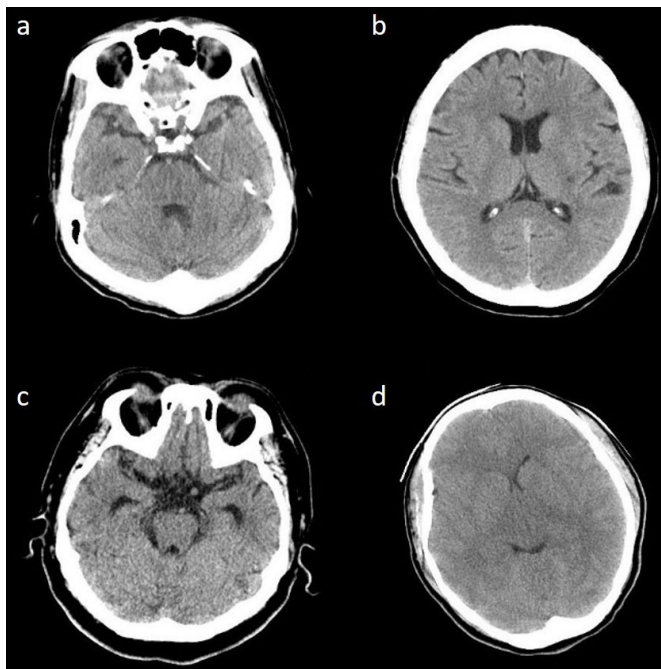


FIGURE 1. CT images of four patients who had an abnormal CT report. (a) The brain CT report revealed a suspected cerebellar infarct. Refer to patient 1 in Table 3. (b) CT report revealed a suspected small infarct. Refer to patient 2 in Table 3. (c) CT report revealed a lacunar infarct and a possible left middle cerebral artery aneurysm at M1 segment. Refer to patient 3 in Table 3. (d) CT report revealed cerebral edema and increased intracranial pressure. Refer to patient 4 in Table 3.

numbers of cases and discrepant treatment indications, we did not include midazolam or other antiepileptic drugs in the efficacy comparison.

4. Discussion

In this study, approximately two-thirds of adult patients with a suspected DSS underwent brain CT despite the absence of head trauma, focal neurological symptoms, or focal seizures. Few of these brain CT scans (6.25%) had abnormal findings. Some of these abnormalities led to further imaging studies but

ultimately had no major impact on clinical management.

The literature reports abnormal emergency CT findings in 34–56% of patients with a first seizure [14–19]. It is generally accepted that brain CT should be performed in patients with a first GTCS. However, few articles have specifically discussed the role of brain CT in DSSs. In a prospective study, 43 of 152 poisoned patients with altered consciousness underwent brain CT, including eight scans done in 13 patients with seizures, and none of these examinations revealed acute abnormalities [2]. Although poisoning may cause intracranial lesions, such as intracranial hemorrhage or cerebral infarction [6], most of these diseases usually have clinical findings, such as focal neurological deficits. In our series, only 1 of the 40 poisoned patients (patient four in Table 3) had abnormal CT findings, which did not result in a significant change in management.

The usefulness of brain CT in alcohol-withdrawal seizures is also debatable. Earnest *et al.* [20] reported intracranial lesions in 16 of 259 (6%) patients with a first alcohol-related seizure and found no correlation with focal neurological symptoms. They regarded CT as an important test in these patients. However, 9 of these 16 patients had a minor head injury or minor focal neurological deficits that met our exclusion criteria. By contrast, Feussner *et al.* [21] found 1% reversible cerebral lesions in patients with suspected alcohol-related seizures who had no neurological symptoms, and concluded that CT does not improve the evaluation of these patients. Schoenenberger *et al.* [15] reported that, in patients who probably had alcohol-related seizures without focal neurological deficit, emergency brain CT may not be absolutely necessary. None of 35 patients with these characteristics in their series had a focal lesion on brain CT. In our study, after carefully excluding patients with a focal neurological deficit or with head trauma, only 3 of 57 patients suspected of having alcohol-withdrawal seizures had abnormal CT findings, and none of these abnormalities had a significant clinical impact.

Benzodiazepines are a commonly used first-line pharmaceutical therapy for DSSs [5, 22]. No randomized controlled study has compared the efficacies of individual benzodiazepines. A Cochrane review of status epilepticus of any cause found that intravenous lorazepam was better than intravenous diazepam for stopping status epilepticus [23]. For alcohol-withdrawal seizures, diazepam seems to have the most favorable phar-

TABLE 4. Anticonvulsants used for seizure treatments and the treatment responses.

Initial anticonvulsant	Patient numbers	Treatment response	
		No more GTCS	Repeated GTCS
Diazepam	25	11	14
Lorazepam	17	11	6
Midazolam	4	4	0
Others AEDs	5	3	2

Abbreviations: GTCS, generalized tonic-clonic seizure; AED, antiepileptic drugs.

macokinetic profile (faster onset and longer half-life) [24], but studies failed to show its superiority over other benzodiazepines [25]. In our study, although patients initially treated with lorazepam had a lower rate of recurrent seizure, the result did not reach statistical significance.

DSS patients who underwent brain CT had a lower initial level of consciousness, higher rate of status epilepticus, and longer hospital stay once admitted. This implies that DSS patients with greater disease severity are more likely to undergo brain CT. This is consistent with several guidelines for new-onset seizures [9–12], and may be strongly related to the clinical risk assessment of emergency physicians.

This study has several limitations. First, it was a retrospective chart review and defined DSS according to the judgement of the emergency physician in charge. DSS cases might have been mistakenly included or excluded. The drug or substance exposure relied highly on the exposure history, which might have been incorrect or misunderstood. Besides, the extent of the physician's suspicion for DSS at the time of deciding to obtain a brain CT could not be well evaluated. Second, cases of DSS are relatively rare and an accurate diagnosis can be difficult. Although this is the largest reported case series, the sample size is still too small to provide strong evidence. Third, the CT abnormalities were based on the formal radiology report, not a dedicated team, which might have led to bias in interpretation.

5. Conclusions

Based on the results of our case series, brain CT examination did not provide additional information in the management of patients with suspected DSSs and did not have concomitant head trauma or significant neurological deficits. Multi-center prospective studies are needed to minimize the bias and obtain stronger evidence.

AUTHOR CONTRIBUTIONS

SFL and MNH designed the study, collected the data and composed the original draft. CHH performed the statistical analysis, composed the original draft. CKC reviewed the chart and collected the data. PCC collected the data and did the data validation. CJS performed the statistical analysis and edited the original draft. HYC designed and supervised the study, reviewed the chart, and edited the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by Chang Gung Institutional Research Board (IRB: 20160883B0).

ACKNOWLEDGMENT

Thank numerous individuals participated in this study, and thanks to all the peer reviewers for their opinions and suggestions.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. At the time of data acquisition, the authors were employed at Keelung branch of Chang Gung memorial hospital, Linkou branch of Chang Gung memorial hospital, and En Chu Kong hospital, Taiwan.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon request.

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How to cite this article: Shao-Feng Liao, Ming-Nan Huang, Cheng-Hsien Hsieh, Chun-Kuei Chen, Po-Cheng Chen, Chen-June Seak, *et al.* Computed tomography for patients with drug- or substance-induced seizures: a retrospective analysis. *Signa Vitae*. 2022;18(1):102-107. doi:10.22514/sv.2021.117.