


# Development of delayed neurologic sequelae in acute carbon monoxide poisoning cases caused by briquette-based kotatsu

## A case-control study

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### Abstract

Briquette-based kotatsu, a traditional Japanese heating system, is still used in rural areas and has been linked to the development of acute carbon monoxide (CO) poisoning. This study aimed to investigate the occurrence of delayed neurologic sequelae (DNS) in patients with acute CO poisoning caused by briquette-based kotatsu.

This retrospective study included 17 patients treated for acute CO poisoning due to briquette-based kotatsu, between April 2017 and March 2020. Patients were divided into either a sequelae group (3 patients) or a non-sequelae group (14 patients) based on the presence or absence, respectively, of DNS. Demographic data, kotatsu characteristics, clinical findings, and therapies were compared between the 2 groups.

Significant differences were noted in patient posture during their initial discovery. Specifically, all non-sequelae patients only had their legs under the kotatsu quilt and all sequelae patients had their entire bodies under the kotatsu quilt ( $P = .001$ ). There were no statistically significant differences in carbon monoxide levels in hemoglobin (CO-Hb) or the creatine-kinase myocardial band (CK-MB), between the 2 groups; however, troponin-I levels were significantly higher in the sequelae group ( $P = .026$ ). Abnormal head imaging findings were noted in 2 sequelae-group patients, with a significant difference between the groups ( $P = .025$ ).

We speculate that acute CO poisoning, caused by briquette-based kotatsu, may lead to DNS more frequently in patients in who cover their entire body with the kotatsu quilt and are found in this position. Patients should be warned about the dangers of acute CO poisoning when using briquette-based kotatsu.

**Abbreviations:** ATA = atmospheres absolute, BE = base excess, CK = creatine kinase, CK-MB = creatine kinase myocardial band, CO = carbon monoxide, CO-Hb = CO in hemoglobin, CT = computed tomography, DNS = delayed neurologic sequelae, ECG = electrocardiogram, GCS = Glasgow Coma Scale, Hb = hemoglobin, HBOT = hyperbaric oxygen therapy, HDS-R = Hasegawa dementia rating scale revised edition, LDH = lactate dehydrogenase, MRI = magnetic resonance imaging, SpCO = percutaneous concentration of CO, WBC = white blood cell count.

**Keywords:** briquette, carbon monoxide poisoning, delayed neurological sequelae, kotatsu

## 1. Introduction

Acute carbon monoxide (CO) poisoning can occur due to malfunctions in heating systems or water heaters, vehicle emissions, or fires and can sometimes lead to delayed neurologic

sequelae (DNS) or even death. DNS<sup>[1]</sup> are reported to occur in 5% to 26% of patients after CO poisoning and are characterized by the presence of a clinically silent or lucid intervals, lasting about 2 to 6 weeks after exposure,<sup>[1,2]</sup> and followed by the

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article [and its supplementary information files];

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**Figure 1.** Kotatsu system. The briquette (A) is put into a specialized container (B) and placed in a hole made in the floor at the bottom of a kotatsu system (C). A table is then placed above and covered with a quilt, and people sit with their feet and legs under the table (D).

development of DNS, including a broad spectrum of neurological deficits, cognitive impairments, and affective disorders.<sup>[3]</sup> However, the mechanisms underlying DNS remain unclear. Briquettes are a source of CO and have been reported to be involved in suicide cases<sup>[4]</sup> and accidental cases<sup>[5]</sup> of CO poisoning. In Japan, briquettes have historically been used as a fuel source in kotatsu, a traditional heating system for the winter season, unique to that country. Briquettes are inexpensively available for bulk purchase from home centers and on the internet, and have a continuous burning-time of about 8 hours.

In this heating method, one briquette (Fig. 1A) is put into a specialized container (Fig. 1B) and then placed into a hole in the floor at the bottom of the kotatsu system (Fig. 1C). A table is then placed above the hole and covered by a quilt, people sit with their feet and legs under the quilt for warmth (Fig. 1D). In recent years, the use of briquette-based kotatsu has decreased in Japan due to the development of electricity-based kotatsu; however, it is still used in rural areas.<sup>[6]</sup>

Some studies have revealed various clinical predictors of DNS upon emergency department admission, including a Glasgow Coma Scale (GCS) score of <9, seizures, systolic blood pressure <90 mm Hg, elevated creatine phosphokinase concentration, leukocytosis, and a positive Babinski reflex.<sup>[1,7,8]</sup> However, these findings remain inconclusive. On the other hand, no previous reports have investigated the relationship between DNS and the context of the acute CO poisoning. The kotatsu system results in an increased risk of severe acute CO poisoning, and the subsequent development of DNS, because of the confined space of CO-exposure.

Therefore, in this article, we aimed to investigate the occurrence of DNS in acute CO poisoning cases caused by briquette-based kotatsu.

## 2. Methods

### 2.1. Study design, ethical considerations, and patient population

This retrospective case-control study included patients diagnosed with acute CO poisoning due to briquette-based kotatsu who were transported to, and treated at, the Emergency and Critical Care Medical Center of Fukushima Medical University Hospital in Fukushima, between April 2017 and March 2020. This study was conducted in compliance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the School of Medicine at Fukushima Medical University (approval number: 2019–305) prior to study enrollment.

Patients were divided into either a sequelae or a non-sequelae group based on the presence or absence, respectively, of DNS occurring between the initial instance of acute CO poisoning and the study endpoint, which was 2 months after acute CO poisoning.

For this study, DNS was defined as the development of any new neurological symptom or signs within 12 weeks of being discharged from the hospital, including motor deficits, cognitive decline, parkinsonism, or seizures. Patients were informed of possible DNS symptoms and were provided contact information to notify researchers if DNS developed after discharge. In addition,

the Hasegawa dementia rating scale revised edition (HDS-R) was used as a patient assessment prior to discharge. The HDS-R is a reliable and brief evaluation that assesses global cognitive function through measures of orientation, memory, attention/calculation, delayed recall, and verbal fluency.<sup>[9]</sup> The maximum total possible score on the HDS-R is 30 points, with lower scores indicating possible cognitive impairment and a score of  $\leq 20$  generally defined as suspected dementia. We performed the HDS-R again 12 weeks after being discharged, and patients with a decrease of 10 points or more were diagnosed as having DNS.

## 2.2. Study variables

Anonymized clinical data were obtained from medical review. The following variables were compared between the 2 groups: age; sex; estimated duration of kotatsu use; body parts covered by kotatsu quilt at the time of discovery; presence or absence of loss of consciousness; percutaneous concentration of CO (SpCO) at the scene of poisoning; GCS score; laboratory data (including white blood cell count [WBC], hemoglobin [Hb], creatine kinase myocardial band [CK-MB], troponin-I, pH, base excess [BE], lactate, and concentration of CO in hemoglobin [CO-Hb]); presence or absence of abnormal head computed tomography (CT) or magnetic resonance imaging (MRI) findings; and presence or absence of hyperbaric oxygen therapy (HBOT) at the medical institution. In addition, we identified patient-reported reasons for using briquette-based kotatsu.

SpCO measurements were obtained using pulse CO-oximeters (Rad-57, Masimo Japan, Inc., Tokyo, Japan). CO-Hb measurements were obtained using a blood gas analyzer (ABL800 FLEX blood gas analyzer, Radiometer Japan, Co., Ltd., Tokyo, Japan). HBOT (BARA-MED, KOIKE MEDICAL, Co., Ltd., Tokyo, Japan) was performed in cases where the CO-Hb level was  $\geq 25\%$ , as well as in cases where syncope was observed in the field despite a CO-Hb level of  $< 25\%$ .

HBOT consisted of 2 sessions on the first day followed by 1 session on subsequent days, for a total of 5 sessions. A HBOT session was comprised of a 15-minute period of compression in air, followed by a 60-minute treatment period at 2.0 atmospheres absolute (ATA), and then a 10-minute decompression period in oxygen. At the discretion of attending physicians, HBOT was performed up to 10 times for patients in whom abnormal findings were identified on CT or MRI examinations or in whom there were minimal improvement in level of consciousness.

## 2.3. Statistical analysis

The Mann–Whitney *U* test was used to compare continuous data between groups, and the chi-square test was used to compare categorical data between groups. Continuous variables are expressed as median plus range and categorical variables are expressed as frequencies and proportions. A *P*-value of  $\leq .05$  was considered to be statistically significant. All statistical calculations were performed using Statcel for Windows, 3rd edition (OMS Publication, Tokyo, Japan).

## 3. Results

Acute CO poisoning occurred in 52 patients within the aforementioned period. We identified 20 patients who experienced acute CO poisoning secondary to use of briquette-based kotatsu. Out of these, we excluded 3 patients, 2 of whom died and 1 of whom did not receive a follow-up. In total, 17 patients

met the entry criteria for this study, with 4 men and 13 women and a median age of 85 years (range, 54–94 years). Three patients were enrolled in the sequelae group, and 14 patients were enrolled in the non-sequelae group (Fig. 2).

The duration of CO exposure could be estimated in 6 patients. The median exposure time was 210 minutes in the non-sequelae group ( $n=5$ ), and the longest exposure time was 405 minutes in the sequelae group ( $n=1$ ). All non-sequelae group patients had only their legs under the kotatsu quilt at the time of discovery, while all sequelae group members had their whole bodies, including their heads, under the kotatsu quilt, with a significant difference observed between groups ( $P=.001$ ). The SpCO level was measured in 11 patients, and the sequelae group tended to have a higher level than the non-sequelae group (40% vs 21%, respectively). On the contrary, there were no statistically significant differences in CO-Hb levels between the sequelae and non-sequelae groups (9.7% vs 13.0%, respectively). Loss of consciousness was identified in 2 (67%) patients in the sequelae group and 5 (36%) patients in the non-sequelae group, with no statistically significant difference.

There were no statistical differences identified in CK-MB levels. On the contrary, the median troponin-I level was 0.204 ng/mL in the non-sequelae group and 0.211 ng/mL in the sequelae group, with a significant difference between the 2 groups ( $P=.026$ ). Abnormal head CT/MRI findings were noted in only 2 patients in this study, both in the sequelae group, with a significant difference identified between the 2 groups ( $P=.025$ ). HBOT was performed a median of 1 time (range, 0–5 times,  $n=8$ ) in the non-sequelae group and a median of 10 times (range, 2–11 times, all cases) in the sequelae group (Table 1).

Patients reported several reasons for using briquette-based kotatsu. Some noted that briquettes were cheaper than kerosene and could be used for a longer period of time and even during electric power failures. In addition, most patients reported understanding the risk of acute CO poisoning during use of briquette-based kotatsu; nevertheless, they were more accustomed to a briquette-based kotatsu and continued to use it despite recommendations to use electrical-based kotatsu instead. Some had even been asked to stop using briquettes by their families.

## 4. Discussion

Our study shows that all patients in the sequelae group had their entire bodies covered by the kotatsu quilt at the time of discovery. On the contrary, all patients in the non-sequelae group had only their legs covered.

Though not statistically significant, SpCO levels tended to be higher in the sequelae group. Both CO concentration and the length of exposure have been shown to be important factors determining the severity of acute CO poisoning.<sup>[10,11]</sup> CO binds more strongly to hemoglobin than oxygen, shifting the oxyhemoglobin dissociation curve to the left and inducing direct hypoxic damage to tissue due to lack of oxygen delivery. Onodera et al<sup>[12]</sup> examined the relationship between the CO exposure time and SpCO levels at the site of CO poisoning and reported that SpCO levels were significantly and positively correlated with the exposure time. On the other hand, CO exposure in enclosed spaces, such as inside homes, has specifically been associated with severe neurological symptoms and heart failure.<sup>[10,13]</sup> Lam et al<sup>[10]</sup> examined patients living in communities in the Guatemalan highlands who used wood-fired temazcals (sauna baths) and reported a positive correlation between SpCO levels and duration

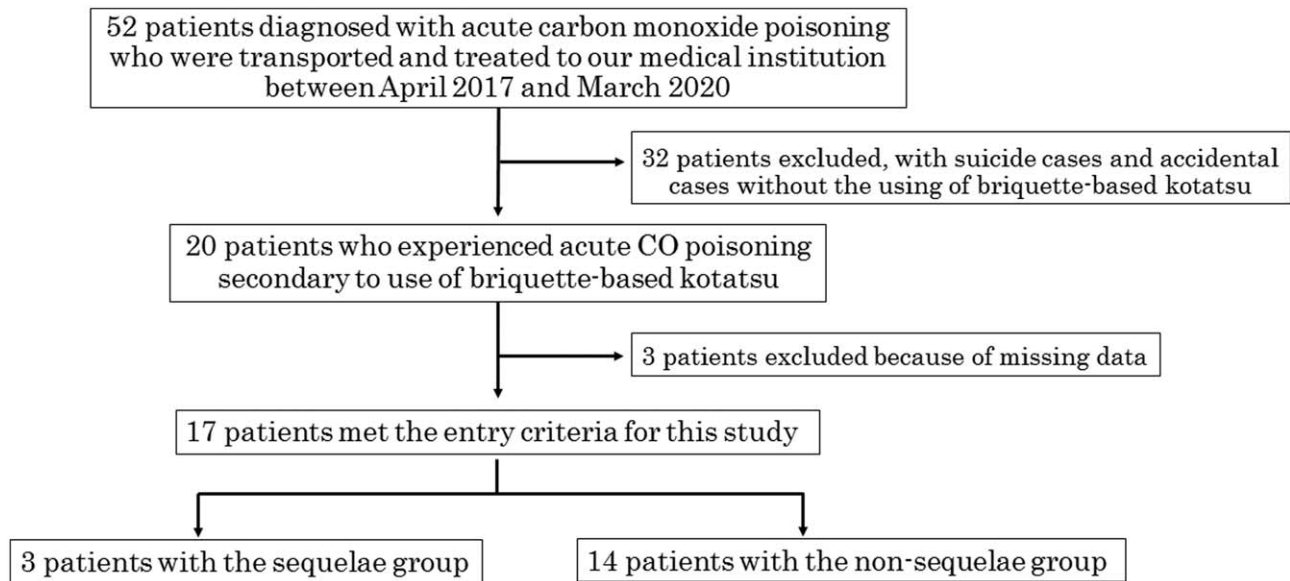


Figure 2. Flow chart showing study identification and selection.

of temazcal use. Additionally, Topacoglu et al<sup>[14]</sup> examined 20 male volunteers who worked at indoor parking lots and carwash facilities and measured their SpCO levels before and after work, consequently concluding that their mean CO-Hb levels were significantly higher due to the exhaust fumes. These results suggest that CO exposure in a confined space can result in more severe poisoning. The current findings support our hypothesis that CO inhalation in a very narrow space, such as while the entire body is under the kotatsu quilt, can induce more severe hypoxic damage and promote the occurrence of sequelae.

In this study, troponin-I was significantly elevated in the sequelae group ( $P=.026$ ). In acute CO poisoning, there is a tendency for organs with high oxygen demand, including the brain and the heart, to incur more severe damage.<sup>[15]</sup> It has

previously been reported that elevated CK-MB and troponin-I levels indicate myocardial injury in patients with acute CO poisoning.<sup>[15–18]</sup> Henry et al<sup>[18]</sup> followed 230 patients who had experienced moderate to severe CO poisoning and reported that 85 (37%) patients developed cardiomyopathies, with elevated levels of troponin-I and CK-MB and abnormal electrocardiogram (ECG) findings. In addition, Marchewka et al<sup>[15]</sup> examined 75 patients with acute CO poisoning and reported that troponin-I levels were significantly correlated with CO exposure time. This suggests that troponin-I levels are associated with the severity of CO poisoning, similar to our findings.

In the present study, there was a significant difference in troponin-I levels between the 2 groups, with no significant difference in CK-MB levels. Some studies have reported that a

Table 1

Differences in clinical characteristics between sequelae group and non-sequelae group.

Characteristics	Sequelae group (n = 3)	Non-sequelae group (n = 14)	P value
Age, y	59 (54–76)	89 (66–94)	.016
Sex (male/female)	1 (33%)/2 (67%)	3 (21%)/11 (79%)	.579
Estimated duration of CO exposure time, min	405 (n = 1)	210 (120–720, n = 5)	.453
Body parts covered with kotatsu quilt (full body/legs)	3 (100%)/0 (0%)	0 (0%)/14 (100%)	.001
SpCO (%)	40 (n = 1)	21 (8–39, n = 10)	.205
CO-Hb (%)	9.7 (0.50–20.6)	13.0 (1.2–26.5)	.313
Loss of consciousness (presence/absence)	2 (67%)/1 (33%)	9 (64%)/5 (36%)	.728
Glasgow Coma Scale	11 (10–11)	14 (8–15)	.684
WBC, /mm <sup>3</sup>	14,100 (1300–15,000)	7050 (4300–16,700)	.614
Hb, g/dL	15.1 (11.9–17.6)	12.2 (4.8–15.5)	.165
CK-MB, IU/L	12.7 (6.6–24.6, n = 3)	1.1 (0.70–1.7, n = 7)	.729
Troponin-I, ng/mL	0.211 (0.118–0.537)	0.204 (0.017–0.249)	.026
pH	7.441 (7.435–7.441)	7.425 (7.373–7.489)	.590
BE	−4.0 (−4.0–1.8)	−0.10 (−10.3–3.8)	.313
Lactate, mmol/L	2.6 (1.1–3.2)	1.6 (0.60–6.1)	.501
Abnormal head CT/MRI findings (presence/absence)	2 (67%)/1 (33%)	0 (0%)/14 (100%)	.025
HBOT (times)	10 (2–11, n = 3)	1 (0–5, n = 8)	.038

Continuous variables are expressed as median plus range and categorical variables are expressed as frequencies and proportions.

BE = base excess, CK-MB = creatine kinase myocardial band, CO-Hb = CO in hemoglobin, CT = computed tomography, HBOT = hyperbaric oxygen therapy, MRI = magnetic resonance imaging, SpCO = percutaneous concentration of CO.

higher creatine kinase level is a potential prognostic factors for the subsequent development of DNS in patients with severe CO poisoning.<sup>[7,19,20]</sup> There have been no reports examining changes in CK-MB and troponin-I levels in these patients over time; however, we speculate that differences in the timing of peak blood levels of these substances, may be one factor contributing to our results. Thus, this study suggests that elevated troponin-I levels may indicate myocardial damage and the potential development of neurological sequelae in patients with severe acute CO poisoning, due to a briquette-based kotatsu.

CO-Hb level did not significantly differ between the 2 groups, with a value of 9.7% (range, 0.50–20.6) in the sequelae group and 12.6% (range, 1.2–26.5) in the non-sequelae group. Previous studies have confirmed that CO-Hb level does not correspond with the severity of CO poisoning.<sup>[21–23]</sup> Liao et al<sup>[23]</sup> examined 466 patients with acute CO poisoning and reported that the initial CO-Hb level was not a risk factor for DNS. Hence, this result is thought to be due to the change in the CO-Hb level as a result of the administration of high-flow oxygen by the emergency medical team.

Despite our findings, this study has some limitations. First, only one institution was involved, and the number of cases was small which limits the generalizability of our findings. Secondly, though we predicted that SpCO levels in the sequelae group would be significantly higher than in the non-sequelae group, due to the small sample size, only a non-statistically significant trend toward higher levels was observed in the sequelae group. Hence, further studies measuring SpCO levels in a greater number of acute CO poisoning cases should be performed in the future. In addition, there were few cases in which the exact time of CO exposure was known. Therefore, we were unable to analyze all the factors that could potentially lead to DNS, and these factors should be investigated in future studies.

In this study, we also examined patient-reported reasons for using briquette-based kotatsu. Patients reported that briquettes had several advantages, including low cost, longer burning times, and the ability to be used during electric power failures. In addition, the price of kerosene, the main fuel for heating appliances, was noted to be increasing. Hence, it is necessary to raise awareness in the population about the risk of acute CO poisoning during the use of briquette-based kotatsu.

## 5. Conclusion

This study demonstrated that DNS occur more frequently in patients who have experienced acute CO poisoning due to briquette-based kotatsu if their entire bodies are covered by the kotatsu quilt at the time of discovery. Hence, we conclude that patients should minimize the extent to which they cover their bodies with the kotatsu quilt.

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## Author contributions

Makoto Onodera: Conception and design of the study, Drafting of the article, and Critical revision of the article for intellectual content.

Zenda Rie, Ueno Satoshi, and Sugaya Kazuki: Analysis and interpretation of data.

Tsukada Yasuhiko, Suzuki Tsuyoshi, Sorimachi Kotaro, Ebihara Kenichi, and Sato Lubna: Collection and assembly of data. Iseki Ken: Final approval of the article.

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