

Case Report

Intracranial Hemorrhage in Methanol Toxicity: Challenging the Probable Heparin Effect during Hemodialysis

Hossein Hassanian-Moghaddam¹, Hooman Bahrami-Motlagh², Nasim Zamani¹, Seyed Amirhossein Fazeli³, Behdad Behnam⁴

¹Toxicological Research Center, Department of Clinical Toxicology, Loghman-Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

²Department of Radiology, Loghman-Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

³Department of Internal Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

⁴Brain Mapping Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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INTRODUCTION

Methanol, a flammable colorless liquid, is commonly used in industry and household solvents while it can also be present in liquors manufactured illicitly. Formate is the key metabolite responsible for metabolic acidosis and symptoms related to methanol poisoning.^[1] Methanol toxicity can lead to death if it is not diagnosed and treated early. Patients usually manifest with nausea, vomiting, blurred vision, seizure, and even coma within 72 h after methanol consumption.^[2] On both computed tomography (CT) scan and magnetic resonance imaging, methanol toxicity is commonly characterized by putamen and white matter necrosis.^[3,4]

Brain hemorrhages are considered as rare complications of acute methanol poisoning.^[5,6] There

ABSTRACT

Brain hemorrhages are rare complications of acute methanol poisoning. There is a debate on association of brain hemorrhage in methanol toxicity and application of systemic anticoagulation during hemodialysis (HD). A 70-year-old male presented to us with severe metabolic acidosis and a methanol level of 7.6 mg/dL. Ethanol and folinic acid were administered, and HD was performed. Brain computed tomography (CT) scan which was normal on presentation showed extensive bilateral subcortical supratentorial hypodensities on the 3rd day after commencing the treatment. However, the next CT scan performed 2 weeks later revealed expanding hemorrhagic transformation in previous hypodensities. Hemorrhagic changes could not be explained by patient's coagulation profile on the 3rd day. Anticoagulation agents such as heparin are used routinely during a dialysis session to prevent clot formation in dialysis circuits. This case is possibly questioning the role of heparin in hemorrhagic brain lesions of methanol intoxication.

KEYWORDS: Hemodialysis, heparin-induced thrombocytopenia, intracranial hemorrhage, Methanol, toxicity

is a debate on the association of brain hemorrhage in methanol toxicity and application of systemic anticoagulation during hemodialysis (HD).^[5,6] Previous studies report a brain hemorrhage rate of 13.5%–16.4% in methanol-poisoned patients on presentation, but there are limited studies on patients who developed hemorrhages after presentation with on-arrival normal imaging studies.^[7] We present an interesting case to review brain CT scanning of a methanol-intoxicated patient in different time intervals before and after conventional HD.

Address for correspondence:

Dr. Hossein Hassanian-Moghaddam, E-mail: hassanian@sbmu.ac.ir

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CASE REPORT

A 70-year-old man was referred to our toxicology department due to suspected methanol toxicity. In the local hospital, he had presented with drowsiness. His family had claimed that he had drunk alcohol about 7 h before presentation. His past medical history was positive for hypertension (HTN), dyslipidemia, and Alzheimer's disease, and his medication history included hydrochlorothiazide 25 mg twice daily, metoprolol 25 mg twice daily, atorvastatin 80 mg daily, lorazepam 2 mg daily, and citalopram 10 mg daily. There was no history of trauma or recent infectious disease. He was a chronic alcohol abuser and cigarette smoker (30 packs/year).

On physical examination, he was in afebrile comatose state with poorly controlled blood pressure of 140/80 mmHg, pulse rate of 85/min, and O₂ saturation of 95%. His pupils were midsize and reactive to light bilaterally without any nystagmus. Deep tendon reflexes were absent, and plantar reflexes were extensor. Other examinations were normal, and laboratory tests were not significant except for hyperglycemia and metabolic acidosis.

On arrival, the patient underwent orotracheal intubation due to his low level of consciousness and metabolic acidosis. Table 1 summarizes important laboratory findings simultaneous with imaging. Initial brain CT scan on presentation was normal. However, the next CT on the 3rd day depicted extensive bilateral subcortical hypodensities in the supratentorial area. Subsequent CT scan on day 14 revealed hemorrhagic changes in previous hypodensities which showed marked deterioration after another week [Figure 1].

Based on methanol level (7.6 mg/dl, normal: 0.2–3 mg/dl), history, and clinical manifestations, the diagnosis of methanol toxicity was confirmed.

Therefore, ethanol 20% gavage (800 mg/kg bolus dose followed by 130 mg/kg/h via nasogastric tube), folinic acid (50 mg intravenous [IV] every 6 h), and NaHCO₃ infusion (2 meq/kg IV followed by 25 meq/h IV infusion) were initiated. Almost 2 h postarrival in our referral center, HD through jugular catheter was applied in 2 consecutive days for 4 h (JMS dialyzer machine, anticoagulant: heparin, buffer: bicarbonate, filter: high flux). The patient received his medications to control HTN during hospitalization, and his blood pressure was within normal range.

Despite appropriate treatment and supportive care, the patient did not show any improvement in his level of consciousness. He was admitted and stayed in intensive care unit for about 3 months until he died. No autopsy was performed. Written informed consent was taken from the patient's next of kin for case report.

DISCUSSION

Herein, we report a case of late intracranial hemorrhage after methanol toxicity to discuss probable mechanism of hemorrhage in this poisoning.

As reported by Sanei Taheri *et al.*^[8] and Vyas *et al.*,^[4] intracranial hemorrhages including putaminal hemorrhage and subcortical necrosis are of the complications that occur rarely with unknown mechanism and have been associated with high mortality rates. Phang *et al.*^[9] reported 6 of 21 patients and Giudicissi *et al.*^[5] reported one case with brain hemorrhagic necrosis after HD, suggesting a deleterious role of systemic anticoagulation during HD.

Heparin is the most common anticoagulation agent used for dialysis. Although it may increase the risk of the central nervous system (CNS) bleeding, its short half-life and available antidote (protamine sulfate) which rapidly restores normal coagulation profile promote large use of

Table 1: Serial venous blood gas, electrolytes, and coagulation profile

Variables	On arrival	2 h	4 h	8 h	3 rd day	14 th day	21 st day
pH	7.2	7.21	6.72	6.95	7.47	-	-
pCO ₂ (mmHg)	24.9	24.4	53.4	48.7	43.4	-	-
HCO ₃ (mEq/L)	8.8	8	7	10.8	31.3	-	-
pO ₂ (mmHg)	37.2	42	104.6	96.6	93.6	-	-
Base excess	-17.8	-21.6	-28.8	-21.4	7.5	-	-
Blood sugar (mg/dL)	245	-	-	-	152	92	118
Serum sodium (mEq/L)	146	-	143	-	138	135	140
Serum potassium (mEq/L)	4.4	-	4.8	-	3.2	4.1	4.4
Serum chloride (mEq/L)	100	-	42	-	-	-	-
Blood urea nitrogen (mg/dL)	10	-	14	-	13	18	21
Creatinine (mg/dL)	1.3	-	1.3	-	0.8	0.8	0.9
Prothrombin time (s)	-	-	-	14	14	13	13
Partial thromboplastin time (s)	-	-	-	32	30	33	30
Platelet (/μL)	-	-	-	96,000	115,000	112,000	104,000

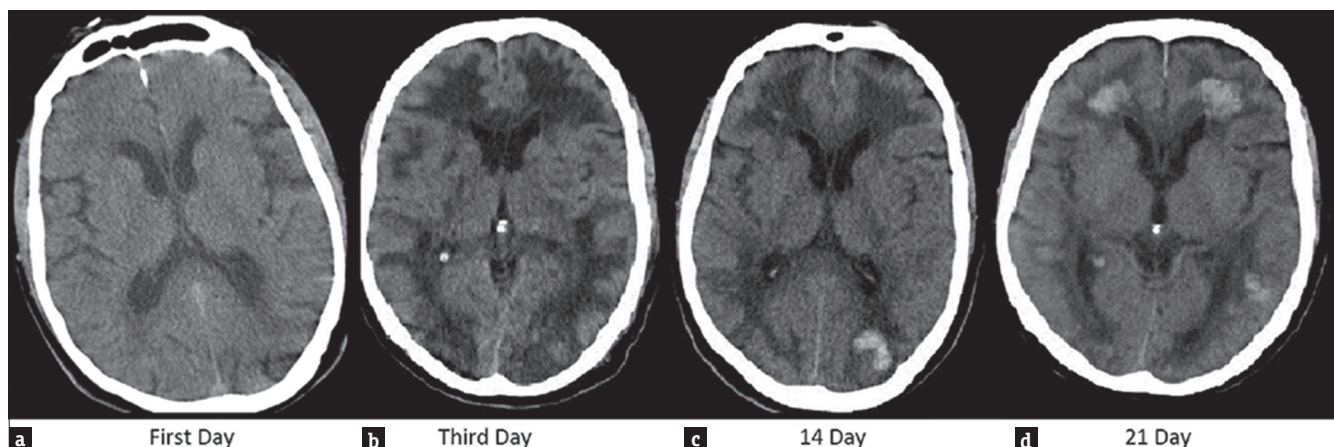


Figure 1: Brain computed tomography scanning of the methanol-poisoned patients in different intervals. First day computed tomography scan (a) is unremarkable. In day 3, (b) there is extensive symmetric hypodensity involving periventricular white matters. Further hemorrhagic transformation present in left occipital lobe in computed tomography scan done in day 14 (c) which has progressed to involve frontal and parietal lobes depicted in computed tomography scan done 21 days after admission (d)

heparin as a safe anticoagulation agent for the dialysis even in high-risk conditions such as methanol poisoning.

Cerebral hemorrhage related to methanol poisoning is usually bilateral and not expansive.^[7] Our patient had a high blood sugar, severe metabolic acidosis, and mild thrombocytopenia with normal coagulation time before HD, and HD was performed with systemic heparinization in the dialysis circuit.

Bleeding is one of the most common side effects of any anticoagulant. The preexisting necrosis in the brain, heparin, and chronic uncontrolled HTN could increase the risk of bleeding and promote the hemorrhagic transformation. Whether such hemorrhagic event was a bleeding diathesis directly due to anticoagulation by heparin or a pure hemorrhagic transformation following acute alcohol ingestion is the main question. A prolonged activated partial thromboplastin time (aPTT) and peripheral ecchymosis can be in favor of heparin role. However, aPTT is not a sensitive and reliable predictor for bleeding.^[10]

In the current case, the 14-day interval between HD sessions and the onset of the first episode of the intracranial hemorrhage, the normal coagulation profile, and the lack of other symptoms significant for heparin-mediated bleeding in skin and other organs may rule out the role of heparin as the initial trigger for bleeding. However, a contributing role can be considered for heparin as well as chronic uncontrolled HTN.

The patient's mild thrombocytopenia might be caused by alcohol intoxication or as a sequel of underlying alcoholic chronic liver disease.^[11] No evidence of thrombocytopenia such as skin petechial rashes or wet purpura of buccal mucosa was found. Furthermore, the platelet counts in our case were not severely low (below 5000–10000)

predisposing to life-threatening bleeding such as intracranial hemorrhage. Given these findings, thrombocytopenia could not be the main culprit initiating the hemorrhagic process in the preexisting necrotic areas. However, in the context of prior CNS lesions, thrombocytopenia can contribute to CNS bleeding diathesis.

In a recent study by Zakharov *et al.*, no association was found between brain hemorrhage and systemic anticoagulation during dialysis. However, bleeding complications occurred in 27% of their patients during treatment. They suggested that high doses of heparin or low molecular weight heparin could apparently facilitate bleeding in necrotic areas of brain.^[12] Aisa and Ballut did not show any relation between methanol-associated CNS hemorrhage and heparin used in HD, either.^[13] In agreement with their study, this case is questioning the role of heparin in hemorrhagic brain lesions of methanol intoxication.

Early CNS bleeding following a dialysis session may be attributed to anticoagulation methods used in the dialysis. However, given the short half-life of heparin, delayed intracranial hemorrhage, as seen in our patient, can be induced by methanol toxicity itself. It seems that alternate anticoagulation strategies cannot reduce the risk of bleeding.

AUTHORS' CONTRIBUTION

Hossein Hassanian-Moghaddam contributed in the concept and design of the study. Hooman Bahrami-Motlagh revised intellectual contents. Behdad Behnam and Seyed Amirhossein Fazeli acquired data and review the literature and contributed in manuscript preparation. Nasim Zamani, Hossein Hassanian-Moghaddam and Hooman Bahrami-Motlagh edited the manuscript. All authors had substantial role in manuscript review.

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Conflicts of interest

There are no conflicts of interest.

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