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SYSTEMATIC REVIEW

Extracorporeal membrane oxygenation in carbamate (methomyl) intoxication: systematic review of the literature and case presentation

Hye-Young Kim[1], Jun-Seok Kim[2], Song-Am Lee[2], Hyun-Keun Chee[2], Jae-Joon Hwang[2], Jin-Yong Kim[3], Michael Ji[4], Yo-Han Kim[5], Woo-Surng Lee[5,*]

[1]Department of Anesthesia and Pain Medicine, School of Medicine, Konkuk University, Konkuk University Chungju Hospital, Chungju-si, Chungbuk, Republic of Korea
[2]Department of Thoracic and Cardiovascular Surgery, School of Medicine, Konkuk University, Konkuk University Seoul Hospital, Seoul, Republic of Korea
[3]Department of Emergency Medicine, School of Medicine, School of Medicine, Konkuk University, Konkuk University Chungju Hospital, Chungju-si, Chungbuk, Republic of Korea
[4]Department of Critical Care Medicine, University of Calgary, Calgary, Alberta, Canada
[5]Department of Thoracic and Cardiovascular Surgery, School of Medicine, Konkuk University, Konkuk University Chungju Hospital, Chungju-si, Chungbuk, Republic of Korea

***Correspondence**
timesgoby@naver.com
(Woo-Surng Lee)

Abstract

Background and Objective: Since methomyl shows a highly significant toxicity, the clinical outcome of acute methomyl pesticide intoxication is extremely critical. Methomyl is a kind of carbamate poisons. Similar to intoxications with other carbamate insecticides, methomyl intoxication inhibits the activity of acetylcholinesterase, which is contained within synaptic junctions between neurons. Most of the methomyl intoxication cases present with symptoms of cholinergic excess, which provokes respiratory failure, cardiovascular failure, and/or cardiorespiratory failure. Methomyl poisoning in humans has not yet been fully evaluated and most studies have reported sporadic cases or series of intoxication. Methomyl poisoning remains a continuing challenge, because this difficult-to-treat clinical condition is frequently associated with significantly high mortality and morbidity. We evaluated the usefulness of extracorporeal membrane oxygenation in the treatment of methomyl intoxication. **Methods**: A systematic literature review was conducted using the PRISMA guidelines without language restriction. We searched for scientific publications via PubMed, Embase, Cochrane central register of controlled trial, Google Scholar, the KoreaMed, and the Research Information Sharing Service database. The goal of this study was to report on incidence, associated complications, and morbidity/mortality of methomyl poisoning, and to draw special attention to its management with extracorporeal membrane oxygenation. **Results**: Only 1 case of a child treated with extracorporeal membrane oxygenation for carbamate or organophosphate intoxication was identified in the literature. After carbamate or organophosphate intoxication, the patient suffered from severe complications including neurological deficits, renal insufficiency, and severe respiratory failure. This child was treated with continuous hemofiltration and extracorporeal membrane oxygenation, but expired after 38 days of extracorporeal membrane oxygenation. In case of our patient, he recovered from the methomyl intoxication after 7 days of VA-ECMO. **Conclusions**: With only a few exceptions, acute methomyl poisoning is potentially life-threatening and has high incidences of morbidity and mortality. Therefore, physicians should keep in mind the possibility of extracorporeal membrane oxygenation for the quick support of intoxication. Extracorporeal membrane oxygenation support might be an alternative to overcome the cholinergic excess, such as respiratory failure, cardiovascular failure, and/or cardiorespiratory failure, especially in the case of severe acute methomyl intoxication.

Keywords

Poisoning; Intoxication; Organophosphate intoxication; Methomyl; Toxicity; Extracorporeal membrane oxygenation; Extracorporeal Circulation; Respiratory therapy; Extracorporeal life support; Oxygenation; Extracorporeal membrane; Oxygenators; Membrane; Pesticides; Acaricides; Herbicides; Insecticides; Rodenticides

1. Introduction

The original cardiopulmonary bypass was developed for adequate blood oxygenation during cardiac surgery, and extracorporeal life support was first employed for the management of acute respiratory distress syndrome in neonates. Over the past several decades, this groundbreaking device has considerably progressed, and the innovative instrument is currently accepted

as an invaluable tool for treating critical patients, especially those suffering from serious respiratory and/or cardiac failure refractory to conventional management. Although there have been several reports that extracorporeal membrane oxygenation (ECMO) support is life- saving in patients with severe acute poisoning, it is extremely difficult to determine what patient should be managed with ECMO support, when ECMO support should be applied, and when ECMO support should be stopped. Because ECMO can only afford supportive therapy rather than disease-modifying treatment, patient selection is essential for the best ECMO outcome. Furthermore, ECMO support requires specialized expertise resources as well as considerable financial support; and physicians and centers frequently encounter ethical issues as well as dilemmas on proper patient selection for ECMO support. Despite remarkable advances in ECMO and critical care management, application of ECMO support for the treatment of acute poisoning is beyond the scope of our investigation. Like our presentation, the majority of reports are on a single case, and only a few excellent review articles are available on this abstruse issue. In patients with acute intoxication, definite determination of the natural history, and efficacy or alteration in invasive ECMO procedures is still lacking [1–5]. We investigated the organophosphate and carbamate intoxication cases treated with extracorporeal life support and/or ECMO. We reported our case of a patient with methomyl intoxication who was successfully treated using venoarterial (VA) ECMO along with detailed systematic literature review.

2. Materials and methods

2.1 Literature review

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6]. We searched for the following articles in accordance with the PRISMA reporting checklist. The relevant articles were collected according to a standardized protocol; the objectives and exclusion/inclusion criteria were specified in detail. We systematically scrutinized the issues related using the following databases: The PubMed, Embase, Cochrane Library (Cochrane Central Register of Controlled Trial), Google Scholar, Springer, Science Direct, KoreaMed, OvidSP, Dialnet, J-Stage, and Scielo and the Research Information Sharing Service database. Scientific publications were searched using the following keywords: “Poisoning” [Mesh] OR “Organophosphate Poisoning ” [TW] OR “Toxicity” [TW] OR “Methomyl” [TIAB] AND/OR “Chemically-Induced Disorders” [TIAB] AND/OR “Drug-Related Side Effects” [TIAB] AND/OR “Methomyl” [TIAB] AND/OR “Toxicity” [TIAB] OR “Extracorporeal Membrane Oxygenation” [Mesh] OR “ECMO” [TW] OR “Vascular System Injuries” [TW] OR “Femoral Vessel Injury” [TW] OR “Vascular Fistula” [TW] OR “Extracorporeal Circulation” [TIAB] OR “Respiratory Therapy” [TIAB] AND/OR “Oxygenators” [TIAB] AND/OR “Membrane” [TIAB] AND/OR “Extracorporeal Life Support” [TIAB] AND/OR “Extracorporeal Membrane” [TIAB] OR “Pesticides” [Mesh] OR “ECMO” [TW] OR “Extracorporeal Circulation” [TIAB] OR “Acaricides” [TIAB] AND/OR “Herbicides” [TIAB] AND/OR “Insecticides” [TIAB] AND/OR “Rodenticides” [TIAB]. Two investigators (corresponding author, WS Lee and first author, HY Kim) independently evaluated the eligibility of relevant abstracts or full articles, and all pertinent references of the articles written in any kind of language were also reviewed. No date restriction was applied to the journal evaluation. In cases of disagreement between the 2 investigators, further discussions were made with a third investigator (co-author, SA Lee). The initial data were evaluated on August 1, 2019 and the final journal search was performed on December, 31, 2019. Only 1 case report was found, without any randomized control clinical trials or comparative studies [7]. Information on the nature of poisoning, time to presentation, cholinergic excess symptoms, clinical course, initial management, continuous ICU treatment including ECMO/continuous renal replacement therapy (CRRT)/ventilator support, neurologic condition, and mechanism of intoxication was analyzed. Exclusion criteria were as follows: (1) other co-ingestion drugs such as cardiovascular drugs, antipsychotics, antidepressants, beta blockers, diltiazem, amlodipine, flecainide, digoxin, and hydrocarbons; (2) other mechanisms of poison exposure including carbon monoxide, carbon dioxide, and smoke inhalation; (3) other unusual types of intoxication such as bitter almonds and methanol; and (4) addiction to drugs such as opioids, narcotics, and cocaine.

2.2 Ethics statement

This study was approved by the Institutional Ethics Committee/Review Board of Konkuk University Chungju Hospital, which waived the requirement for informed patient consent due to its retrospective study design (IRB approval no., KUCH 2020-02-005).

2.3 Statistical analysis

As all of the data collected were case reports. The universal statistical analysis was not possible, so that only descriptive statistic evaluations were presented in this study.

2.4 Case presentation

A 63-year-old man presented to the Emergency Department (ED) in an unconscious state after a sip of beverage containing a carbamate pesticide whose main ingredient was methomyl. He had no remarkable history of specific diseases or operations except for hypertension which was being successfully treated with calcium-channel blockers at a regional hospital for 20 years. While talking with his wife and relatives, he ingested the beverage accidentally and suddenly became unconscious after a few minutes. His wife witnessed small and involuntary muscle contractions, which were suspected as fasciculations. She found a bottle of methomyl on the ground and took it to the physician. Cardiopulmonary resuscitation (CPR) was quickly initiated by a bystander for over 10 minutes until hospital arrival. At the ED, he was in a comatose mental state, and his Glasgow coma scale (GCS) score was 4 points: eye response, 1; verbal response, 1; and motor response, 2.

TABLE 1. Laboratory findings.

	Reference	Unit	ADM	HD #1	HD #2	HD #3	HD #4	HD #5 ECMO weaning initiation	HD #6	HD #7 ECMO weaning	HD #8	HD #9	HD #10	HD #11 PDT	HD #12 ventilator weaning	HD #13 CRRT weaning	HD #28 discharge
WBC	3.5-10.0	$\times 10^3$/uL	10.26	22.23	21.19	20.76	16.01	14.22	17.45	23.82	25.31	28.93	31.13	25.39	20.05	16.35	9.8
RBC	3.5-4.9	$\times 10^6$/uL	3.97	3.7	3.89	3.67	3.33	3.38	3.32	3.14	2.95	3.06	2.95	2.68	2.72	3.01	3.48
Hb	11.0-15.0	g/dL	17.3	11.5	12	11.4	10.3	10.4	10.2	9.9	9.3	9.7	9.3	8.4	8.6	9.4	11
Hct	34.3-45.3	%	37.3	33.7	34.4	33.2	29.7	29.7	29.5	27.8	26.5	27.4	27.2	24.9	26	27	32
Platelet	149-394	$\times 10^3$/uL	226	249	149	116	109	129	137	138	154	172	179	202	277	286	311
AMN	11-31	mmol/L	65.3	70.9	80.6	85.6	78.8	71.1	58.8	50.9	43.5	39.8	36.7	29.9	27.7	26.1	24.3
SGOT	7-38	IU/L	24	131	393	▲5000	▲3877	▲1226	▲475	232	140	132	108	119	132	98	45
SGPT	4-43	IU/L	23	90	237	▲5000	▲4190	▲3078	▲2056	▲1319	▲852	▲760	▲575	378	312	146	62
Glu	75-99	mg/dL	196	321	152	190	175	160	95	218	253	241	218	203	189	176	133
BUN	5-22	mg/dL	15.4	16.9	14.9	22.4	23.8	24.5	28.9	37.5	42.4	43.7	49.9	49	43	40.2	28.2
Cr	0.6-1.2	mg/dL	1.39	1.39	1.15	1.46	1.63	1.46	1.47	1.61	1.57	1.58	1.72	1.65	1.43	1.4	1.18
TB	0.2-1.1	mg/dL	0.7	0.5	2.7	3	3.7	5.6	7	7.2	7.4	9	8.1	7.9	7.6	6.5	1.4
DB	0-0.6	mg/dL	na	na	na	na	na	na	na	4.3	4.4	na	5	5	4.7	3.9	0.3
T-PRO	5.8-8.1	g/dL	7.4	4.4	1.2	1.3	1.8	2.9	3.9	4.5	4.6	4.9	4.9	5.2	5.2	5.3	6.5
ALB	3.1-5.2	g/dL	4.4	2.7	2.8	2.6	2.3	2.4	2.5	2.5	2.5	2.6	2.6	2.7	2.7	2.8	3.3
P	2.5-5.5	mg/dL	6.1	4.1	3.2	3.7	3.3	4	4.3	4.7	3.6	4	3	2.7	2.5	2.5	3.2
Ca	8.2-10.8	mg/dL	9.8	6.5	7.8	7.8	7.8	8.4	9.1	8.7	8.6	8.8	8.7	8.7	8.7	8.6	9.4
CRP	0-0.5	mg/dL	0.37	0.26	0.77	2.99	▲7.08	▲10.31	▲10.55	▲10.65	▲12.26	▲13.83	▲15.55	▲16.16	▲14.05	10.89	3.21
AML	37-220	U/L	57	68	62	59	55	57	78	59	64	88	108	127	99	89	80
r-GTP	0-30	IU/L	108	114	na	na	na	na	123	na	na	na	236	na	na	166	42
LDH	263-450	IU/L	1230	1325	1402	1449	1897	1656	1400	1234	1152	1140	1109	960	868	697	401
CPK	50-200	U/L	897	725	1002	999	928	656	79	79	66	60	46	44	46	40	39
Na	138-148	mmol/L	139	135	136	139	140	140	139	137	134	135	137	140	145	139	140
K	3.5-5.3	mmol/L	3.9	3.8	3.5	3.7	3.7	3.9	3.6	4.3	3.8	3.8	3.4	3.6	3.9	3.7	3.8

TABLE 1. Continued.

	Reference	Unit	ADM	HD #1	HD #2	HD #3	HD #4	HD #5	HD #6	HD #7	HD #8	HD #9	HD #10	HD #11	HD #12	HD #13	HD #28
								ECMO weaning initiation		ECMO weaning				PDT	ventilator weaning	CRRT weaning	discharge
Cl	98-108	mmol/L	96	104	104	106	108	108	107	106	103	103	105	110	115	106	109
OSM	274-301	mOsm	286	289	290	300	298	299	296	299	298	294	299	298	298	295	294
CK-MB	0-4.0	ng/mL	1.6	20.2	22.4	6.1	2.2	0..8	0.6	1	1.1	1.3	1.2	2.5	1.9	1.3	0.9
BNP	0-100	pg/mL	5	260	445	409	398	377	301	260	211	205	199	179	108	110	102
Ti	0-0.015	ng/mL	0.01	0.64	17.62	6.53	1.51	0.9	0.57	0.51	0.33	0.25	0.24	0.19	0.16	0.13	0.02
pH	7.35-7.45	–	6.98	7.33	7.45	7.38	7.48	7.54	7.51	7.51	7.5	7.47	7.41	7.44	7.44	7.44	7.45
pO_2	80-100	mmHg	6	185	166	62	83	73	94	86	103	89	81	123	136	142	122
pCO_2	35-45	mmHg	81	24	20	35	35	27	24	25	28	28	30	29	29	37	39
BE	-6	mmol/L	-9.7	-11.7	-8.3	-3.9	0.5	1.1	-3.4	-2.3	-0.9	-2.5	-4.8	-3.8	-3.9	1.1	1.2
Glu	60-110	mg/dL	186	295	144	169	168	177	64	176	196	226	230	184	223	176	133
Lactate	0.5-2.2	mmol/L	9.5	6.1	4.4	3.9	2.8	2.3	2.2	3.9	4.2	4.4	3.4	3.1	2.4	2	2
PT	9.1-13.9	sec	11.3	20.4	28.4	32.4	30.1	19.9	19	15	13.8	12.3	13.7	13	12.9	11.7	12.1
aPTT	25.1-36.5	–	22.3	68.4	80.1	60.4	40.2	38.4	38	35.3	39.9	32.6	36.9	28.3	27.9	29.8	31.8
INR	0.85-1.29	sec	1.1	2	2.6	3	2.7	1.9	1.8	1.4	1.3	1.1	1.2	1.2	1.2	1.1	1.2
D-dimer	0-255	ng/mL	▲9112	▲8987	▲8121	▲7934	▲5758	▲3321	▲2888	▲1784	▲1323	▲989	▲911	▲665	▲454	321	221
AT-III	70.0-125.1	%	68	60.1	44.4	33.6	25	48.4	50.6	59	58.4	60.8	68.9	68.4	69.6	70	74
FDP	0-2.01	μg/mL	▲51.8	60.8	42.8	38.8	20.7	19.8	19.6	12.8	9.8	8.7	7.8	6.8	5.1	4.8	3.2

The arrowheads indicate more than 10-fold increases over the upper reference level. Abbreviations: ADM, admission day; HD, hospital day; ECMO, extracorporeal membrane oxygenation; PDT, percutaneous tracheostomy; CRRT, continuous renal replacement therapy; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; AMN, ammonia; SGOT, serum glutamate oxaloacetic transaminase; SGPT, glutamate pyruvate transaminase; Glu, glucose; BUN, blood urea nitrogen; Cr, creatinine; TB, total bilirubin; DB, direct bilirubin; T-PRO, total protein; ALB, albumin; P, phosphate; Ca, calcium; CRP, C-reactive protein; AML, amylase; r-GTP, gamma-glutamyltransferase; LDH, lactate dehydrogenase; CPK, creatine phospho kinase; Na, sodium; K, potassium; Cl, chloride; OSM, osmolarity; CK-MB, creatine kinase; BNP, brain natriuretic peptide; Ti, Troponin I; BE, base excess; PT, prothrombin time; aPTT, activated partial thromboplastin time; INR, international normalized ratio; AT-III, anti-thrombin-III; FDP, fibrin degradation product; na, not available.

His blood pressure, pulse rate, and respiratory rate could not be checked. His body temperature was 35.8 °C, and oxygen saturation measured using a pulse oximeter was uncheckable. By means of guideline on airway management with intubation, breathing under Intermittent positive-pressure ventilation with 100% oxygen, circulation under closed cardiac compressions, and drugs with atropine/adrenaline etc., continuous cardiopulmonary cerebral resuscitation (CPCR) restored spontaneous circulation (ROSC), but the spontaneous circulation lasted for less than 30 seconds and re-arrest (RA) appeared. Repeated vicious circles of arrest, CPCR, ROSC, and RA occurred. To overcome these vicious circles, ECMO support was employed. Extracorporeal cardiopulmonary resuscitation was successfully performed using Seldinger's technique with the aid of ultrasound, a venous cannula was placed just below the right atrium via the femoral vein, and an arterial cannula was placed in the iliac artery via the femoral artery. After successful extended CPR treatment with VA-ECMO, the patient dramatically recovered from the arrest state, showed normal sinus rhythm; however, he unfortunately remained in a semicomatose state. Following VA-ECMO, his blood pressure became 95/60 mmHg, pulse rate 30 beats/min, respiratory rate 6 times/min, body temperature 35.8 °C, and oxygen saturation 92%. Finding of portable chest anterior-posterior radiographs were compatible with acute respiratory distress syndrome. He had pin-point pupils and increased bronchial secretions. Physical examination revealed severe cholinergic symptoms such as salivation, lacrimation, urination, defecation, bradycardia, bronchospasm, and bronchorrhea. Under a confirmative diagnosis of methomyl intoxication, atropine and pralidoxime were immediately administered. Atropine was injected as a bolus and its dosage doubled every 3 to 5 minutes until bronchial secretions and wheezing resolved: an initial loading dose of 2.0 mg via the intravenous (IV) route; after 5 minutes, a loading dose of 4.0 mg; after another 5 minutes, a loading dose of 8.0 mg (total loading dose of 14 mg [2.0 + 4.0 + 8.0 mg] until stabilized); and a maintenance dose of 1.4 mg/hour. Oxime therapy with pralidoxime was given as a dose of 2.0 via the intravenous route for 30 minutes as a loading dose and continuous IV infusion (8.0 mg/kg/hour) as a maintenance dose. Diazepam 10 mg was intravenously administered for seizure control. During ECMO, he was managed with hypothermia therapy by maintaining body temperature at 33 °C -34 °C for 24 hours and administering sedatives such as midazolam, remifentanil, dexmedetomidine, or diazepam. Laboratory tests and clinical findings revealed a series of cardiorespiratory failure, acute renal failure, and hepatic failure, and then the patient's condition deteriorated rapidly due to multiorgan failure, showing leukocytosis, thrombocytosis, anemia, hyperbilirubinemia, increases in liver parameters, hypoalbuminemia, inflammation, amylase increase, hyperammonemia, and elevated D-Dimers. The laboratory test results are described in Table 1. For the confirmative diagnosis of methomyl poisoning, red blood cell (RBC) acetylcholinesterase (AChE) activity is essential, which is not available in our center. Only the plasma level of cholinesterase, also known as butyl-cholinesterase (Bu-AChE) or pseudo-cholinesterase, is able to be measured in our center. The initial level of plasma cholinesterase was 839 (reference level, 10,000-12,900). He was meticulously managed in the intensive care unit (ICU) using mechanical ventilation, and CRRT, VA-ECMO, especially for the multi-organ failure. His clinical course in the ICU was uneventful, and thus VA-ECMO was successfully weaned on the seventh day. Percutaneous tracheostomy was performed on the 11th hospital day, the ventilator was weaned on the 12th hospital day, and CRRT was weaned on the 13th hospital day. On the 14th hospital day, diffusion-weighted magnetic resonance imaging of brain with susceptibility-weighted imaging and fluid attenuated inversion recovery revealed bilateral diffusion restrictions in occipital white matters, basal ganglia, thalami, tail of corpus callosum, and symmetric subcortical hypersignal, presented as metabolic encephalopathy. Despite aggressive treatment, his consciousness state was in a drowsy to stupor state, which was probably because structural changes in the AChE-organophosphorus compound led to no response to antidotal oxime and the final level of Bu-AChE was 3,608. On the 28th hospital day, he was transferred to the general ward of rehabilitation and then to a regional hospital with incomplete recovery from methomyl intoxication.

3. Results

Twenty-nine published studies were carefully evaluated. Of the 29 studies, 21 were excluded and the remaining 8 were subjected to our analysis, with only 1 met the study criteria. Thus, 2 studies that include 1 previously published case and ours were systematically reviewed (Fig. 1). One case of a child treated with ECMO for carbamate intoxication was identified in the literature. After methomyl intoxication, the patient had severe clinical signs, including neurological deficits, renal insufficiency, and severe respiratory failure. This child was treated with continuous hemofiltration and ECMO, but expired after 38 days of the treatment. Our patient also presented severe cholinergic excess, which provoked cardiorespiratory his symptoms were similar to those of failure, and showed cholinergic symptoms similar to methomyl intoxication, including muscarinic and nicotinic manifestations. He also showed neurological deficits, renal insufficiency, and severe respiratory failure. He was treated with antidote along with administration of atropine and pralidoxime, hypothermia, mechanical ventilation, continuous renal replacement therapy, and ECMO. He recovered from the intoxication after 7 days of VA-ECMO. In spite of active treatment with VA-ECMO, his conscious level on discharge day was identified as a drowsy to stupor state, and a failure to full recovery to normal consciousness was related not only to acute poisoning, but also to cerebral ischemia after cardiac arrest, concerned with insufficient atropine administration.

4. Discussion

The insecticide methomyl has the following features: Chemical Abstracts Service (CAS) Registry Number, 16752-77-5: chemical name, S-methyl N-(methylcarbamoyloxy) thioacetimidate; chemical formula, C5H10N2O2S; molecular weight, 162.20; appearance, white crystalline solid; odor, slight sulfur-like; and melting point, 78 °C to 79 °C. It was first introduced by E.I. du Pont de Nemours in 1968 and was classified as a

TABLE 2. Characteristics and physicochemical properties of methomyl.

Features	Values
CAS No	16752-77-5
CIPAC No	264
Molecular formula	$C_5H_{10}N_2O_2S$
Chemical names in IUPAC	*S*-methyl *N*-[(methylcarbamoyl) oxy]thioacetimidate
Molecular weight (g/mol)	162.2
Density at 25 °C (g/mL)	1.29
Melting point (°C)	78-79
Octanol-water partition coefficient (log *K*ow)	1.24
Organic carbon normalized partition coefficient (*K*oc)	72
Vapor pressure at 25 °C (mmHg)	5.6×10^{-6}
Henry's law constant (Pam^3mol^{-1})	2.13×10^{-6}
LC_{50} values (50% lethal concentration)	
Rats	17 to 45 mg/kg
Bluegill sunfish and rainbow trout	0.9 to 3.4 mg/L
Daphnia magna	0.022 to 0.026 mg/L
Solubility at 25 °C (g/L)	
Water	57.9
Methanol	1,000
Acetone	730
Ethanol	420
Isopropanol	220
Toluene	30
Hydrolysis characteristic	Half-life, hydrolytically stable at 25 °C at pH 5 and 7
	Half-life, 30 days at 25 °C at pH 9
Photolysis characteristics	No direct photolysis observed when exposed to 365 nm artificial sunlight
	365 nm artificial sunlight

Abbreviations: No, number; CAS, Chemical Abstract Service registry; CIPAC, Collaborative International Pesticides Analytical Council; IUPAC, International Union of Pure and Applied Chemistry; Koc, Organic carbon normalized partition coefficient; LC50 values, 50% lethal concentration.

restricted-use pesticide by the US Environmental Protection Agency (EPA) in 1978 (Table 2). Methomyl is one of the carbamate insecticides that acts as a cholinesterase inhibitor and controls a broad spectrum of agricultural and household insects. It is a representative broad-spectrum carbamate insecticide which is mainly used to prevent and control pests. It is also known as lannate, mesomile, methomex, or nudrin. Methomyl is one of the most commonly used carbamate insecticides worldwide. Methomyl has a nature of white solid with sulfur smell and is soluble in water, acetone, ethanol, methanol, and other organic solvents. Methomyl pesticide is generally stable in water, so that a mixture of water and methomyl pesticide is grossly indistinguishable from water alone, which has frequently led to water-borne outbreaks [8]. It might gain access to the body not only through the respiratory tract, but also via the skin or digestive tract [9–11]. Methomyl has highly significant toxicities, and its 50% lethal dose (LC_{50} value) is reported to be 17-45 mg/kg in rats. In general, the clinical outcome of acute methomyl pesticide intoxication is poor, and human exposure to methomyl causes 3 different degrees of toxic reactions according to the exposure route: oral exposure, highly toxic; inhalation, moderately toxic; and dermal exposure, slightly toxic. It is also highly toxic to mammals, fish, and aquatic invertebrates [12].

Similar to intoxications with other carbamate insecticides, methomyl intoxication usually inhibits the activity of AChE in synaptic junctions between neurons. When acetylcholinesterase is inhibited, the hydrolytic deactivation of acetylcholine is completely blocked, which continuously stimulates postsynaptic receptors to cause nerve and tissue failures. Most of the human vital functions are controlled by the peripheral nervous system, and inhibition of these functions can be fatal in mammals. Methomyl poisoning in humans has not been fully understood, and most studies have reported sporadic cases or series of methomyl poisoning occurring accidentally as well as for suicide. The toxic effect in methomyl intoxication is considered to be perioxidative damage to hepatic, renal, and splenic

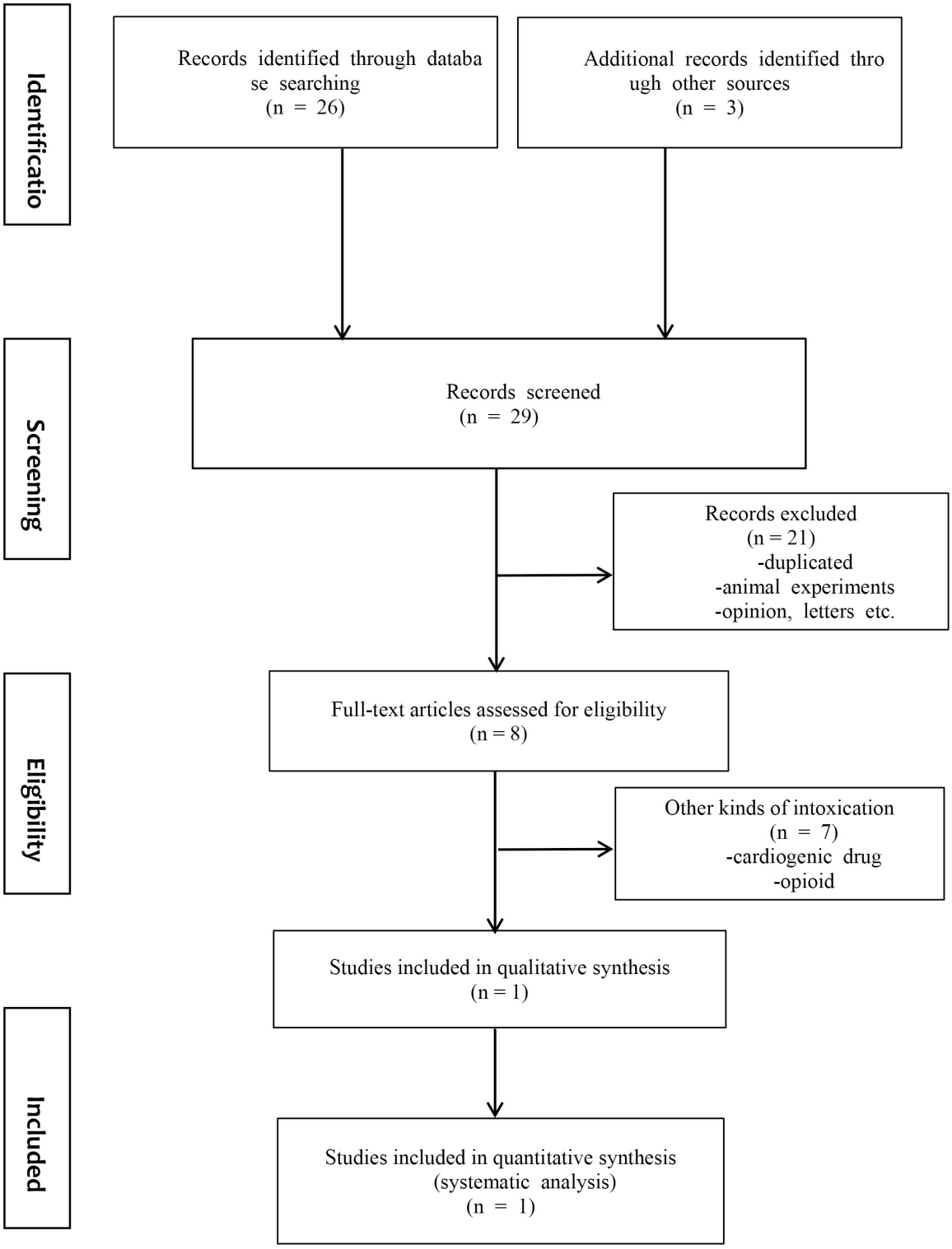

FIGURE 1. Flow diagram of the study selection process.

cell membranes as well as DNA damage to these organs [13]. Nicotinic effects in methomyl intoxication are summarized as follows: fasciculation, muscle weakness, paralysis, depolarization due to the action of succinylcholine, central nervous and respiratory dysfunction, seizures, and unconsciousness. Generally, carbamate is less toxic than organophosphate compounds because of relatively short-term cholinesterase inhibition and rapid cholinesterase inhibitor enzyme reactivation. Actually, acute symptoms of carbamate intoxication, such as methomyl intoxication, are very similar those of cholinergic excess observed in the case of organophosphate compound intoxication. However, there is no significant difference in mortality and morbidity between carbamate and organophosphate compound intoxications [14, 15]. Therefore, for a better understanding of methomyl intoxication, it is essential to consider both carbamate and organophosphate compound intoxications. Most of these toxic materials were banned in the United States in 2001.

Unfortunately, organophosphate could not be completely withdrawn from the market or banned from use due to its wide use. Especially in developing countries, it is more widely used for effective crop and vegetable protection with its advantages (1) in eliminating a broad spectrum of insects, (2) no effect on seed activity, (3) considerable cost-effectiveness, and (4) small amounts of residue on food grains [16, 17]. Several organophosphorus agents, such as tabun, sarin, and soman, were initially developed in Germany during the 1940s, the Second World War, for military purposes. The main mechanism of organophosphate toxicity is associated with neutered AChE which it renders a non-functional form. Acetylcholinesterase is the main enzyme responsible for hydrolyzing acetylcholine into choline and acetic acid, and organophosphorus compounds friendly bind with RBC AChE. Inactivated acetylcholinesterase leads to acetylcholine accumulation at neuronal synapses and neuromuscular junctions, bringing about reluctance to AChE reactivation over exposure time. Conformational change of acetylcholinesterase-organophosphorus compound is reported as aging, which render AChE irreversibly resistant to reactivation by the antidote oxime. In addition, neuropathy target esterase (NTE) are inhibited by organophosphate. However, the clinical significance of their inhibitions and interactions have not yet been fully evaluated [18].

Carbamate compounds are mainly derived from carbamic acids. Similar to organophosphorus agents, carbamate is rapidly absorbed via various exposure routes including the skin, lungs, and gastrointestinal tract. Unlike organophosphate, carbamate is a transient cholinesterase inhibitor and spontaneously hydrolyzes at the cholinesterase enzymatic site within 48 hours. However, a clear differentiation between organophosphate and carbamate intoxications is essential in clinical practice because both of them show relatively similar features. Carbamate toxicities may have shorter duration than toxicities caused by equivalent doses of organophosphate, despite similar mortality rates between subjects exposed to organophosphates and carbamate [16]. Medical applications of the carbamate compounds echothiophate, pyridostigmine, tacrine, and donepezil include reversal of neuromuscular blockade, by neostigmine or pyridostigmine/edrophonium, and treatment of glaucoma, myasthenia gravis, and Alzheimer disease. The major respiratory effects of carbamate intoxication are neuromuscular depression, bronchospasm, excessive secretion, and respiratory failure. Cardiovascular collapse or cardiorespiratory failure could be fatal, although its exact mechanism is not completely understood. Primary cardiac effects are heart block, ischemia, QT prolongation, prolonged arrhythmia, and cardiac arrest. It is not clear whether these cardiac arrhythmias are caused by direct toxicity or secondary hypoxemia [19]. Renal damage, such as acute kidney injury or acute tubulointerstitial nephritis, is relatively common and may occasionally require intermittent hemodialysis or continuous renal replacement therapy. Gastrointestinal damage, such as pancreatitis, is also uncommon.

Clinical features of carbamate intoxication generally manifest within minutes or hours after exposure, and most of the acute toxicities are related with cholinergic excess. Cholinergic excess symptoms of the intoxications can be summarized as the so-called SLUDGE-BBB: salivation, lacrimation, urination, defecation, gastric emptying, bradycardia, bronchospasms, and bronchorrhea. Other cholinergic excess symptoms are summarized as the so-called DUMBBELS: diarrhea, urination, miosis/muscle weakness, bronchorrhea, bradycardia, emesis, lacrimation, and salivation/sweating. During the period of acute toxicity, respiratory insufficiency and failure may result from respiratory muscle weaknesses, decreased respiration drives from the central nervous system, increased secretions, and bronchospasm. The symptoms of carbamate intoxication occur just 24 to 96 hours after exposure. Bulbar, respiratory, and proximal muscle weaknesses generally resolve within 1 to 3 weeks after exposure. Within several weeks after organophosphate exposure, delayed peripheral neuropathy (OPIDN) usually occurs, primarily involves motor function, resolves spontaneously, but may result in permanent neurological deficits.

A diagnosis of carbamate intoxication is based on clinical features. The clinical features of cholinergic excess should initially be considered as the possibility of carbamate poisoning, even in the absence of ingestion or exposure history. Some of the carbamate agents have characteristic petroleum- or garlic-like odor, which might be helpful in establishing the diagnosis. In clinical practice, carbamate intoxication is suspected in patients who present with the absence of anticholinergic signs, such as tachycardia, mydriasis, decreased bowel sounds, and dry skin. In patients suspected of carbamate ingestion, 1.0 mg of atropine in adults (or 0.01 to 0.02 mg/kg in children) should be administered. Atropine challenge might be helpful and life-saving, especially if a definite diagnosis is difficult to make. Diminution in signs and symptoms by anticholinergic effects following atropine administration strongly suggests acetylcholinesterase inhibitor poisoning. RBC AChE activity should be measured to make a confirmative diagnosis of carbamate intoxication. The level of RBC AChE activity is useful for evaluating the degree of toxicity. Serial measurement of RBC AChE activity ca be performed to assess the effectiveness of oxime therapy in reactivating acetylcholinesterase enzyme during chronic or occupational carbamate exposure. However, most hospital laboratories are unable to perform this measurement that requires a specialized high level of laboratory, so they measure plasma- or pseudo-cholinesterase activity instead. However, in the majority of cases, plasma cholinesterase or pseudocholinesterase activity does not completely reflect the severity of carbamate intoxication and should not be used in a standard rescue therapy.

Initial treatment strategies for acute toxicity are respiratory support, with 100% oxygen delivery, early intubation, and avoidance of similar pharmacological drugs such as succinylcholine. In the case of oral ingestion, decontamination with activated charcoal (50 in adult or 1.0 g/kg in children) within 1 hour would be helpful, and dermal and ocular irrigation might also be helpful. The management of carbamate intoxication focuses on treating cholinergic toxicity. Cholinergic toxicity can be treated with 2 rescue medications: one is atropine and the other is pralidoxime. Atropine has strong effects on muscarinic receptors, and tachycardia or mydriasis is not an

absolute contraindication into atropine treatment. It is usually injected as a regimen of bolus doubling dose and should be escalated as a double dose every 3 to 5 minutes until bronchial secretions and wheezing resolve: loading dose, initially 2.0 mg intravenous injection, after 5 minutes 4.0 mg, after another 5 minutes 8.0 mg (total loading dose, 14 mg until atropine saturation; maintenance dose, 1.4 mg/hour). Atropine has profound effects on secretion clearance and bronchospasm relief. In several intoxication cases, hundreds of milligrams of atropine are needed for several days. Pralidoxime exerts effects on main nicotinic and minor muscarinic receptors. Pralidoxime is usually intravenously given as a dose of 2.0 (25 mg/kg in children) for 30 minutes as a loading dose and at a dose of 8.0 mg/kg/hour (10 mg/kg/hour in children) as a maintenance dose. It has significant effects on dissociation of organophosphate and AChE band as well as reactivation of acetylcholinesterase, which terminates the action of the neurotransmitter acetylcholine. The main mechanisms underlying pralidoxime rescue are AChE reactivation, acetylcholine degradation, and consequently decreased acetylcholine concentration. However, atropine has a little different rescue medication effect: competition with an intoxication regimen on acetylcholine receptors. Taken together, both atropine and palidoxime are essential for the treatment of the intoxication. Furthermore, benzodiazepine therapy using intravenous (IV) diazepam 10 mg in adults (0.1 to 0.2 mg/kg in children) should be repeated as if seizures occur [16–19].

The clinical features and characteristics observed in our case are not different from those of a previous case report, except for application of extracorporeal membrane oxygenation to treat respiratory and cardiac failures in methomyl intoxication. ECMO is commonly defined as a device that supports the cardiopulmonary system by adequate oxygenation, carbon dioxide removal, and adequate perfusion in a patient with cardiac and/or respiratory failure. The ECMO unit pumps hypoxic and hypercapnic blood out of a patient's body, runs it through an artificial lung membrane where carbon dioxide is adequately removed and oxygen is supplied, and then returns oxygenated and eucapnic warm blood into the patient's body. In intoxication, ECMO bypass of the heart and lungs permits the heart, lungs, and involved organs to recover from toxic insult and to maintain the delivery of oxygenated, eucapnic, nutritious blood to all tissues while allowing for continual elimination of toxins. To the best of our knowledge, this is the first case report of successful application of extra-corporeal membrane oxygenation for the treatment of respiratory failure and cardiac failure which resulted from methomyl intoxication. Direct evidence originates from case reports, case series, and observational cohort studies. Symptomatic and supportive care still remains the mainstay of intoxication treatment. Extracorporeal membrane oxygenation, a supportive treatment option, would be the most aggressive supportive modality. As previously described, extracorporeal membrane oxygenation is commonly defined as a device that supports the cardiopulmonary system by adequate oxygenation, carbon dioxide removal, and adequate perfusion in a patient with cardiac and/or respiratory failure. This is an external instrument that supports the cardiopulmonary system through sufficient oxygenation and hemodynamic support in a patient with cardiac and/or respiratory failure, caused by various medical and surgical conditions, leading to cardiovascular collapse, respiratory failure, cardiogenic shock, or refractory hypotension. ECMO could be an effective modality of treatment for patients with toxin exposure, because hemodynamics and oxygenation would be supported while the toxin is metabolized and eliminated. ECMO might be helpful in the setting of toxin exposure that results in cardiorespiratory failure or metabolic dysfunction, and for itself does not remove or neutralize any toxins, but provides hemodynamic support and oxygenation until elimination of the toxin or eventual end-organ recovery. ECMO might play a role in managing severe intoxication patients, along with other rescue therapies and supportive interventions.

Numerous human case reports/series have shown considerably favorable outcomes after ECMO application in intoxication patients involving a variety of pharmaceuticals including tricyclic antidepressants, cardiovascular medications, and anti-dysrhythmics such as lidocaine, amitriptyline, verapamil, acebutolol, flecainide, digoxin, disopyramide, diltiazem, and betaxolol. Most of the pharmaceutical exposures in individual cases were similar to those in cases already reported in the literature, leading to cardiotoxicity or hemodynamic collapse. Non-pharmaceutical exposure to non-pharmaceutical agents, such as carbon monoxide, zinc, arsenic, hydrocarbon, and taxus, which requires ECMO as a treatment modality, has been sparingly reported. Despite successful treatment of intoxicated patients with ECMO, it is not clear whether ECMO would improve survival in intoxicated patients and exactly when ECMO should be initiated. ECMO application prior to cardiovascular collapse can improve overall survival. As mentioned above, our case displayed signs of severe toxicity, including metabolic acidosis, seizures, coma, cardiac dysrhythmias, and hypotension, prior to receiving ECMO. An attempt to initiate ECMO during cardiac arrest is extremely difficult because it requires a relatively long time of pauses in cardiopulmonary resuscitation during cannulation. In addition, apart from clinical course of intoxication, ECMO itself is at high risk of potential complications, including limb ischemia, compartment syndrome, stroke, acute kidney injury, bleeding, emboli, and infection. Furthermore, physicians must consider several risk factors in individual patients, such as advanced age, comorbidities, risk for complications, survivability, exposure to specific drugs or chemicals, and duration of hypoperfusion or cardiac arrest. Large amounts of resources are required to perform and manage ECMO, and only a few facilities have the ability to activate ECMO in a timely fashion.

DeLange *et al.* [4] reported 16 patients with toxin-induced refractory shock and acute respiratory distress syndrome requiring ECMO as well as calcium channel antagonists, beta blockers, and hydrocarbons, in their retrospective chart review using the California Poison Control System (CPCS) database from the American Association of Poison Control Centers (AAPCC). They analyzed patients who were treated with ECMO for a wide array of clinical manifestations, such as hypotension (69%), asystole (44%), and respiratory arrest (31%) as well as side effects of cardiovascular drugs such as beta-blockers, diltiazem, amlodipine, flecainide, digoxin, and hydrocarbons. Of the 16 patients who received ECMO, 12 were managed with VA-ECMO and 4 were

treated with venovenous ECMO; 13 (81%) recovered and 3 (19%) died. Wang *et al*. [20] performed a retrospective review of the American College of Medical Toxicology (ACMT) Toxicology Investigators Consortium (ToxIC) for the evaluation of ECMO application in toxin exposure. They evaluated 26,271 patients (male : female, 4 : 6) reported to the ToxIC Registry from January 1, 2010 to December 31, 2013, and found only 10 (0.0038 %) patients receiving ECMO treatment, who were exposed to carbon monoxide/smoke inhalation, bitter almonds, methanol, or several medications, including antihistamines, antipsychotic/antidepressant, cardiovascular drugs, analgesics, sedative/hypnotics, and antidiabetics. They showed the overall survival rate of as high as 80% after treatment with ECMO and concluded that ECMO should be initiated prior to cardiovascular failure. Weiner *et al*. [21] performed clinical analysis of 104 poisoning patients with severe or refractory drug-induced cardiovascular shock who were managed with VA-ECMO, by systematic search of the Extracorporeal Life Support Organization (ELSO) ECMO case registry. The first case of poisoning treated with VAMO occurred in 2009 and the remaining cases had developed until 2017. In the 104 intoxicated patients under ECMO, the most common poison was cardiovascular agents (n = 49, 47.1%), followed by opioids (n = 9, 8.7%), cocaine (n = 4, 3.8%), antidepressants (n = 4, 3.8%), anticoagulants (n = 3, 2.8%), solvents (n = 3, 2.8%), antiepileptics, antineoplastics, hypoglycemic phosphorus (n = 2, 1.9%, respectively), antibiotics, hallucinogen, metals, smoke, propionic acids, carbon monoxide, aminophenol, psychostimulants, and tranquilizers (n = 1, 0.9%, respectively).

In the cases presented, it is not easy to assess why and how the extremely toxic symptoms, such as respiratory failure and cardiac failure, developed just 1-2 minutes after ingestion of a suspected drink. This catastrophic presentation is due partly to quick delivery of the poison absorbed from the stomach to vital organs and partly to the synergism between methomyl and other toxic chemicals.

5. Conclusions

ECMO has rarely been applied in intoxicated patients. ECMO shows a variety of clinical courses. In most cases, including ours, ECMO might be a useful supportive treatment option when administered prior to cardiac arrest, improving survival. Decisions should be made in conjunction with a multidisciplinary team of toxicologists, intensivists, and surgeons. Intoxications by anticholinesterase compounds are not uncommon, and this public health threat should be prevented and completely eradicated by the health authorities. Severe and serious intoxications can be complicated by life-threatening multiorgan failure during and after the initial phase of intoxication, and can progress into prolonged disability or even death. In such intoxications, ECMO support can be an alternative to overcome cholinergic excess symptoms such as respiratory, cardiovascular, and cardiorespiratory failures.

ABBREVIATIONS

AAPCC, American Association of Poison Control Centers; AChE, acetylcholinesterase; ACMT, American College of Medical Toxicology; ADM, admission day; ALB, albumin; AML, amylase; AMN, ammonia; aPTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AT-III, anti-thrombin-III; BE, base excess; BNP, Brain natriuretic peptide; Bu-AChE, butyl-cholinesterase; BUN, blood urea nitrogen; Ca, calcium; CAS, Chemical Abstracts Service; CK-MB, Creatine Kinase MB isoenzyme; Cl, chloride; CPCR; cardio-pulmonary cerebral resuscitation; CPCS, California Poison Control System; CPK, creatine phosphokinase; CPR, cardiopulmonary resuscitation; Cr, creatinine; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; DB, direct bilirubin; ECMO, extracorporeal membrane oxygenation; EDC, emergency department center; ELSO, Extracorporeal Life Support Organization; EPA, Environmental Protection Agency; FDP, fibrin degradation product; GCS, Glasgow coma scale; Glu, glucose; r-GTP, gamma-glutamyltransferase; Hb, hemoglobin; Hct, hematocrit; HD, hospitalization day; ICU, intensive care unit; IRB, Institutional Ethics Committee/Review Board; INR, international normalized ratio; IV, intravenous; K, potassium; LC50, the acute 50% lethal concentration lethal dose; LDH, lactate dehydrogenase; Na, sodium; na, not available; OPIDN, organophosphorus agent-induced delayed peripheral neuropathy; OSM, osmolarity; P, phosphate; PDT, percutaneous tracheostomy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PT, prothrombin time; RA, re-arrest; RBC, red blood cell; ROSC, return of spontaneous circulation; SGOT, serum glutamate oxaloacetic transaminase; SGPT, glutamate pyruvate transaminase; TB, total bilirubin; Ti, Troponin I; T-PRO, total protein; ToxIC, Toxicology Investigators Consortium; VA, veno-arterial; WBC, white blood cell.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The present study was approved by the Institutional Ethics Committee/Review Board of Konkuk University Chungju Hospital, which waived the requirement for informed patient consent due to its retrospective case reporting nature (IRB approval no., KUCH 2020-02-005). All subjects enrolled in this research have given their informed consent, which has been approved by my institutional committee on human and/or animal research, and this protocol has been found acceptable by them.

AUTHORS CONTRIBUTION

HY Kim, JS Kim, WS Lee, SA Lee, JY Kim, YH Kim, CK Chee and Michael JI conceived of and designed the study, collected and interpreted the data, and drafted the manuscript. WS Lee and JS Kim collected and interpreted the data. SA Lee, WS Lee and Michael Ji analyzed and interpreted the data, and performed statistical analyses. WS Lee and JJ Hwang participated in the study design, and revised the manuscript.

WS Lee and Michael Ji critically reviewed the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declared no conflict of interest with respect to the authorship and/or publication of this article.

AVAILABILITY OF DATA AND MATERIAL

The datasets generated and/or analyzed during the present study are available from the corresponding author on reasonable request.

FOOTNOTES

1. Reporting Checklist: The authors have completed the PRISMA reporting checklist.
2. Conflicts of Interest: The authors declared no conflict of interest with respect to the authorship and/or publication of this article. All authors have completed the ICMJE uniform disclosure form.
3. Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
4. Consent for publication: Written informed consent for publication of clinical data and clinical images was obtained from the patient.

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