

# Hemodynamic changes after infusion of intravenous lipid emulsion to treat refractory hypotension caused by glyphosate-surfactant herbicide poisoning

## A case report

Min-Jeong Lee, MD, Young Gi Min, MD\*

### Abstract

**Rationale:** Glyphosate-surfactant herbicides (GlySH) are non-selective herbicides that are extensively used worldwide. A recent case report on GlySH poisoning suggested successful resuscitation upon using intravenous lipid emulsion (ILE) for refractory hypotension. The efficacy of ILE in GlySH poisoning remains unproven due to a lack of randomized controlled trials, and further evidence is required to clarify the mechanism by which ILE may reverse hypotension in GlySH poisoning.

**Patient concerns:** A 46-year-old man presented to the emergency department 45 min following ingestion of approximately 200 cc of GlySH. On arrival, his vital signs were as follows: blood pressure, 82/50 mmHg and pulse, 85 beats/min. Hypotension did not respond to fluid resuscitation and norepinephrine infusion; his cardiac output (CO) was 4.5L/min and systemic vascular resistance (SVR) was 604 dynes·s·cm<sup>-5</sup> with blood pressure of 63/35 mmHg.

**Diagnosis:** GlySH poisoning presented with refractory hypotension.

**Interventions:** A bolus (100 mL) of ILE was infused with subsequent infusion of 400 mL over 4 h.

**Outcomes:** A few minutes following the bolus of ILE, his blood pressure increased to 101/54 mmHg with CO of 6.5 L/min and SVR of 701 dynes·s·cm<sup>-5</sup>. Blood pressure, CO, and stroke volume increased gradually over next 8.5 h. His clinical status improved gradually, and norepinephrine could be tapered on hospital day (HD) 3. The patient was discharged at HD 10 without sequelae.

**Lessons:** ILE could be used as a rescue treatment in case of a poor response to conventional fluid and vasopressor therapy. The underlying mechanism of rescue with ILE might be a positive inotropic effect.

**Abbreviations:** CO = cardiac output, GlySH = Glyphosate-surfactant herbicides, HD = hospital day, ILE = intravenous lipid emulsion, SVR = systemic vascular resistance.

**Keywords:** cardiac output, glyphosate, hypotension, lipid emulsion

## 1. Introduction

Glyphosate-surfactant herbicides (GlySH) are non-selective herbicides that are used worldwide.<sup>[1,2]</sup> Although GlySH is generally considered to have low toxicity,<sup>[3]</sup> large amounts of ingestion may lead to life-threatening toxicity in humans.<sup>[4–6]</sup>

Editor: N/A.

The authors have no funding and conflicts of interest to disclose.

Department of Emergency Medicine, Ajou University School of Medicine, Republic of Korea.

\* Correspondence: Young Gi Min, Department of Emergency Medicine, Ajou University School of Medicine, 164 World cup-ro, Yeongtong-gu, Suwon 16499, Republic of Korea (e-mail: youngmd@me.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:3(e14156)

Received: 12 September 2018 / Received in final form: 18 December 2018 /

Accepted: 25 December 2018

<http://dx.doi.org/10.1097/MD.0000000000014156>

In cases of severe GlySH intoxication, shock and arrhythmia may occur, which often do not respond well to fluid resuscitation or vasopressor administration.<sup>[7]</sup> Treatment for GlySH poisoning is primarily supportive in nature, with no effective antidotes specifically available against shock caused by GlySH. However, a recent case report suggested successful resuscitation using intravenous lipid emulsion (ILE) for refractory hypotension caused by GlySH poisoning.<sup>[8]</sup> In recent cases of a series of GlySH intoxications, ILE administration was associated with a lower incidence of hypotension and arrhythmia relative to the retrospective controls.<sup>[9]</sup> The efficacy of ILE in GlySH poisoning still remains unproven because of a lack of randomized controlled trials, and further evidence is required to clarify the mechanism by which ILE may reverse hypotension in GlySH poisoning. We, here, present a case report of documented hemodynamic changes in a patient with refractory hypotension caused by GlySH poisoning, after ILE administration. Informed written consent was obtained from the patient for publication of this case report.

## 2. Case report

A 46-year-old man presented to the emergency department 45 min following ingestion of approximately 200 cc of GlySH (41% glyphosate, polyoxyethyleneamine surfactant, water, and minor formulation ingredients). He had no history of any major

**Table 1****Hemodynamic changes after infusion of intravenous lipid emulsion.**

Time	16:46	17:50	19:00	20:00	21:00	21:30	22:00	23:00	0:00	01:00	02:00	04:00
SBP (mmHg)	82	89	80	83	63		101	131	136	134	133	148
DBP (mmHg)	50	53	40	54	35		54	75	63	63	66	71
MAP (mmHg)	61	65	53	64	44		69	94	87	88	88	97
HR (beat/min)	85	87	101	104	102		123	123	128	120	123	123
CO (L/min)	–	–	–	–	4.5		6.5	11.4	10.2	9.5	11.8	10.4
SVI (mL/beat)	–	–	–	–	44		53	93	80	79	96	86
SVR (dynes · s/cm <sup>5</sup> )	–	–	–	–	604		701	589	603	656	535	661
CVP (mmHg)	–	5	8	10	10		12	10	10	10	9	11
Norepinephrine (μg/kg/min)	–	0.25	0.47	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55	1.55
Lipid emulsion (ml)	–	–	–	–	–	100 ml bolus	400 ml for 4 h					

CO = cardiac output, CVP = central venous pressure, DBP = diastolic blood pressure, HR = heart rate, MAP = mean arterial pressure, SBP = systolic blood pressure, SVI = stroke volume index, SVR = systemic vascular resistance.

illnesses. On arrival, he had a Glasgow Coma Scale (GCS) score of 13/15. His vital signs were as follows: blood pressure, 82/50 mmHg; pulse, 85 beats/min; respiratory rate, 25 breaths/min; and temperature, 36.2 °C. His weight was 78 kg and physical examination revealed an injected throat and cold extremities with otherwise unremarkable findings. Drug screen was unremarkable, chest X-ray was normal, and an electrocardiogram showed no specific findings. Arterial blood gas analysis showed a pH of 7.28, PaO<sub>2</sub> of 91.7 mmHg, PaCO<sub>2</sub> of 32.3 mmHg, base deficit of –10.5 mmol/L, HCO<sub>3</sub> of 14.9 mmol/L on room air. Serum lactic acid concentration was 3.3 mmol/L. There was no other significant abnormality in electrolytes or routine blood chemistry.

Fluid resuscitation was initiated. The patient remained hypotensive despite aggressive fluid resuscitation, and therefore, administration of norepinephrine was started intravenously at a rate of 0.25 μg/kg/min. The patient was started on continuous veno-venous hemodiafiltration (CVVHDF). At 3.5 h after poisoning, he became obtunded with a GCS score of 5/15. He was intubated and placed on mechanical ventilation. Non-invasive hemodynamic monitor (Vigileo™ monitor; Edwards Lifesciences, USA) revealed a CO of 4.5 L/min and systemic vascular resistance (SVR) of 604 dynes·s·cm<sup>-5</sup> with blood pressure of 63/35 mmHg (Table 1). Because hypotension did not respond to fluid resuscitation and norepinephrine infusion, a bolus (100 mL) of ILE (SMOFlipid 20%; Fresenius Kabi, Germany) was infused with a subsequent 400 mL infusion over 4 h. A few minutes following the bolus of ILE, his blood pressure increased to 101/54 mmHg with CO of 6.5 L/min and SVR of 701 dynes·s·cm<sup>-5</sup>. Blood pressure, CO, and stroke volume increased gradually over next 8.5 h. At 12 h after poisoning, his hemodynamic parameters were as follows: blood pressure, 148/71 mmHg; CO, 10.4 L/min, and SVR, 661 dynes·s·cm<sup>-5</sup>. The clinical status gradually improved and norepinephrine could be tapered on hospital day (HD) 3. The patient was discharged at HD 10 without sequelae.

### 3. Discussion

Our case report describes quantitative hemodynamic changes following ILE in refractory shock caused by poisoning in humans. The key findings of our case are that ILE produced an increase in CO, but not in SVR. Fettiplace et al reported that lipid-emulsions exerted rapid, positive inotropic effects in both intact rat and isolated-heart models.<sup>[10]</sup> Although the definitive mechanism of action is yet to be determined, the likely explanation for improved hemodynamic performance is that plasma free fatty acids

generated from infused lipid provide metabolic substrates for cardiac oxidative phosphorylation.<sup>[11]</sup> Stehr et al reported a significant increase in cardiac performance in a study of bupivacaine toxicity in isolated hearts of rats undergoing lipid perfusion at concentrations too low to support the lipid sink theory.<sup>[12]</sup>

ILE administration did not cause an elevated heart rate, but increased the systolic blood pressure, which may support the role of ILE as an inotropic agent.<sup>[12]</sup> Our results suggest that ILE had direct inotropic effects. Heart rate and stroke volume both increased after ILE initiation, resulting in an increased CO. SVR showed a slight decrease in status and showed no significant changes after ILE initiation.

Another mechanistic possibility, although not mutually exclusive with direct inotropy, is the lipid sink theory.<sup>[13]</sup> Clinically important redistribution of glyphosate seems unlikely, given that it is a small, polar molecule with limited toxicity. The toxic effects observed following ingestion of GlySH formulations are generally attributed to the surfactant.<sup>[4]</sup> The surfactant component, however, has a lipophilic "tail," characteristic of detergent structures, which could plausibly associate with the circulating ILE particles. Studies using radio- or isotope-labeled glyphosate and surfactant, as reported by Weinberg et al,<sup>[14]</sup> are required to clarify whether ILE facilitates redistribution of GlySH components from cardiac myocytes. Clinicians considering ILE infusion should, however, be aware of the potential complications,<sup>[15]</sup> which are likely to make this modality inappropriate for patients with less than serious-to-life-threatening toxicity.

### 4. Conclusion

If shock caused by GlySH poisoning responds poorly to conventional fluid and vasopressor therapy, ILE could be tried as a potential rescue treatment. The underlying mechanism of rescue with ILE may be a positive inotropic effect, although redistributive phenomenon cannot be presently ruled out. We hypothesize that ILE may have a role in treating refractory hypotension caused by GlySH poisoning. Further reports, as well as animal and clinical studies, are required to verify this conclusion.

### Author contributions

**Conceptualization:** Young Gi Min.

**Data curation:** Min-Jeong Lee and Young Gi Min.

**Investigation:** Min-Jeong Lee and Young Gi Min.

**Supervision:** Young Gi Min.

**Writing – original draft:** Young Gi Min.

**Writing – review & editing:** Min-Jeong Lee and Young Gi Min.

## References

- [1] Jauhiainen A, Rasanen K, Sarantila R, et al. Occupational exposure of forest workers to glyphosate during brush saw spraying work. *Am Ind Hyg Assoc J* 1991;52:61–4.
- [2] Lavy TL, Cowell JE, Steinmetz JR, et al. Conifer seedling nursery worker exposure to glyphosate. *Arch Environ Contam Toxicol* 1992;22:6–13.
- [3] USEPA. Glyphosate. In: Registration Eligibility Decision Document. Washington, DC: Special Review and Reregistration Division, Office of Pesticide Programs, 1993.
- [4] Roberts DM, Buckley NA, Mohamed F, et al. A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning. *Clin Toxicol (Phila)* 2010;48:129–36.
- [5] Chen YJ, Wu ML, Deng JF, et al. The epidemiology of glyphosate-surfactant herbicide poisoning in Taiwan, 1986–2007: a poison center study. *Clin Toxicol (Phila)* 2009;47:670–7.
- [6] Lee HL, Chen KW, Chi CH, et al. Clinical presentations and prognostic factors of a glyphosate-surfactant herbicide intoxication: a review of 131 cases. *Acad Emerg Med* 2000;7:906–10.
- [7] Talbot AR, Shiaw MH, Huang JS, et al. Acute poisoning with a glyphosate-surfactant herbicide ('Roundup'): a review of 93 cases. *Hum Exp Toxicol* 1991;10:1–8.
- [8] Han SK, Jeong J, Yeom S, et al. Use of a lipid emulsion in a patient with refractory hypotension caused by glyphosate-surfactant herbicide. *Clin Toxicol (Phila)* 2010;48:566–8.
- [9] Gil HW, Park JS, Park SH, et al. Effect of intravenous lipid emulsion in patients with acute glyphosate intoxication. *Clin Toxicol (Phila)* 2013;51:767–71.
- [10] Fettiplace MR, Ripper R, Lis K, et al. Rapid cardiotoxic effects of lipid emulsion infusion. *Crit Care Med* 2013;41:e156–62.
- [11] Partownavid P, Umar S, Li J, et al. Fatty-acid oxidation and calcium homeostasis are involved in the rescue of bupivacaine-induced cardiotoxicity by lipid emulsion in rats. *Crit Care Med* 2012;40:2431–7.
- [12] Stehr SN, Ziegeler JC, Pexa A, et al. The effects of lipid infusion on myocardial function and bioenergetics in l-bupivacaine toxicity in the isolated rat heart. *Anesth Analg* 2007;104:186–92.
- [13] Weinberg G, Lin B, Zheng S, et al. Partitioning effect in lipid resuscitation: further evidence for the lipid sink. *Crit Care Med* 2010;38:2268–9.
- [14] Weinberg GL, Ripper R, Murphy P, et al. Lipid infusion accelerates removal of bupivacaine and recovery from bupivacaine toxicity in the isolated rat heart. *Reg Anesth Pain Med* 2006;31:296–303.
- [15] Levine M, Skolnik AB, Ruha AM, et al. Complications following antidotal use of intravenous lipid emulsion therapy. *J Med Toxicol* 2014;10:10–4.