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LETTER TO THE EDITOR: PUTATIVE UNDERLYING MECHANISMS OF LIPID EMULSION TREATMENT FOR ALUMINUM PHOSPHIDE POISONING

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To the Editor,

I read with interest the pilot clinical trial "Efficacy of intravenous lipid emulsion as an adjunctive therapy for acute aluminum phosphide poisoning: a randomized, open-label, pilot clinical trial" recently published in *European Review for Medical and Pharmacological Sciences*[1]. I thank the authors for the valuable clinical trials. Lipid emulsions are routinely used to treat local anesthetic systemic toxicity[2]. In addition, lipid emulsions have been reported to alleviate cardiovascular depression induced by toxic doses of non-local anesthetic drugs with high lipid solubility [log (P = octanol/water partition coefficient) > 2][3]. I would like to comment on the underlying mechanism of lipid emulsion treatment as an adjuvant drug for drug toxicity and sample size estimation in future formal randomized controlled trials.

The underlying mechanism of lipid emulsion treatment as an adjuvant drug for drug toxicity involves indirect and direct effect[2]. Lipid shuttling, an indirect mechanism, states that lipid emulsions absorb lipid-soluble drugs (log P: > 2, for example: log P of bupivacaine = 3.41) from the brain and heart[2]. Lipid emulsions with lipid-soluble drugs are transported to the liver, muscle, and adipose tissues for detoxification, and storage[2]. The direct mechanisms include positive inotropic activity, increased fatty acid supply, suppression of mitochondrial dysfunction and nitric oxide release, phosphorylation of glycogen synthase kinase-3β, and reduction of reactive oxygen species production[2]. Adenosine triphosphate (ATP) administered before bupivacaine exposure reduced myocardial depressive effects, suggesting bupivacaine-induced cardiac toxicity may be associated with mitochondrial dysfunction[4]. Bupivacaine inhibits carnitine acylcarnitine translocase, impairing transport of long-chain fatty acids into the mitochondrial matrix and reducing ATP production through fatty acid β-oxidation[5,6]. In addition, bupivacaine induces complex I inhibition of the mitochondrial respiratory chain and uncoupling of oxidative phosphorylation, leading to decreased ATP production[7,8]. However, lipid emulsions attenuate the bupivacaine-induced inhibition of carnitine

acylcarnitine translocase[9]. Lipid emulsions attenuate bupivacaine-induced cardiotoxicity by inhibiting reactive oxygen species production and mitochondrial dysfunction[9,10]. Aluminum phosphide reacts with moisture to release phosphine gas; therefore, its log P is not applicable[11]. In addition, log P of phosphine gas is −0.1, which is hydrophilic[12]. Phosphine gas, which is released from aluminum phosphide in the gastrointestinal tract, induces mitochondrial cytochrome C oxidase inhibition, formation of highly reactive hydroxyl radicals, and oxidative stress, leading to cardiac arrhythmia, intractable shock, and acidosis, similar to cardiac mitochondrial dysfunction caused by bupivacaine toxicity[5,7,8,11]. Thus, considering the hydrophilicity of phosphine gas (log P: −0.1), the direct effects of lipid emulsion—such as attenuation of phosphine-induced mitochondrial dysfunction and oxidative stress—may play a greater role in recovery from aluminum phosphide poisoning than the indirect "lipid shuttle" mechanism associated with lipid solubility.

The authors reported the relative risk of the primary outcome was 0.493 (95% confidence interval: 0.335-0.725)[1]. However, the relative risk based on the obtained data was 0.369 (95% confidence interval: 0.211-0.649).

No formal sample size or power calculations were performed before this randomized open-label pilot study. Based on the observed mortality rates (control group, 62%; lipid emulsion group, 22.9%), an exploratory sample size estimation was performed using a two-proportion Z-test to inform the future randomized controlled trial design. Assuming a two-sided α of 0.05, a power of 80%, a 1:1 allocation ratio, and a 10% dropout rate, the estimated sample size was approximately 27 patients per group. Given that pilot studies may overestimate treatment effects due to small sample sizes, a conservative effect size was assumed for planning future randomized controlled trials. If the mortality rate in the lipid emulsion group was 42%, corresponding to an 20% absolute mortality reduction compared to the control group in aluminum phosphide poisoning, the required sample size would be approximately 107 patients per group. These calculations should be interpreted cautiously as pilot studies are not designed for precise effect estimates.

Considering the above findings, a future multicenter randomized controlled trial is required to evaluate the effect of lipid emulsions on aluminum phosphide poisoning and confirm the results of this pilot study.

Conflict of Interest
The author has no conflict of interest to disclose.

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Data Availability
Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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Ethics Approval and Informed Consent
Not applicable.

REFERENCES

1. Singh Bhatia M, Attri R, Saroch A, Kumar Pannu A, Singla N, Chandrabhan Sharda S. Efficacy of intravenous lipid emulsion as an adjunctive therapy for acute aluminum phosphide poisoning: a randomized, open-label, pilot clinical trial. Eur Rev Med Pharmacol Sci 2026; 30: 27-36.
2. Lee SH, Sohn JT. Mechanisms underlying lipid emulsion resuscitation for drug toxicity: a narrative review. Korean J Anesthesiol 2023; 76: 171-182.
3. Ok SH, Park M, Sohn JT. Lipid Emulsion Treatment of Nonlocal Anesthetic Drug Toxicity. Am J Ther 2020; 28: e742-e746.
4. Eledjam JJ, de La Coussaye JE, Brugada J, Bassoul B, Gagnol JP, Fabregat JR, Massé C, Sassine A. In vitro study on mechanisms of bupivacaine-induced depression of myocardial contractility. Anesth Analg 1989; 69: 732-735.
5. Weinberg GL, Palmer JW, VadeBoncouer TR, Zuechner MB, Edelman G, Hoppel CL. Bupivacaine inhibits acylcarnitine exchange in cardiac mitochondria. Anesthesiology 2000; 92: 523-528.
6. Yu HK, Ok SH, Kim S, Sohn JT. Anesthetic management of patients with carnitine deficiency or a defect of the fatty acid β-oxidation pathway: A narrative review. Medicine (Baltimore) 2022; 101: e28853.
7. Sztark F, Nouette-Gaulain K, Malgat M, Dabadie P, Mazat JP. Absence of stereospecific effects of bupivacaine isomers on heart mitochondrial bioenergetics. Anesthesiology 2000; 93: 456-462.
8. Sztark F, Malgat M, Dabadie P, Mazat JP. Comparison of the effects of bupivacaine and ropivacaine on heart cell mitochondrial bioenergetics. Anesthesiology 1998; 88: 1340-1349.
9. Ok SH, Kang D, Lee SH, Kim HJ, Ahn SH, Sohn JT. Lipid emulsions attenuate the inhibition of carnitine acylcarnitine translocase induced by toxic doses of local anesthetics in rat cardiomyoblasts. Hum Exp Toxicol 2022; 41: 9603271211065978.
10. Yang L, Bai Z, Lv D, Liu H, Li X, Chen X. Rescue effect of lipid emulsion on bupivacaine-induced cardiac toxicity in cardiomyocytes. Mol Med Rep 2015; 12: 3739-3747.
11. Gurjar M, Baronia AK, Azim A, Sharma K. Managing aluminum phosphide poisonings. J Emerg Trauma Shock 2011; 4: 378-384.
12. PubChem. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Phosphine#section=Chemical-and-Physical-Properties. [Accessed on March 11, 2026].