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REVIEW ARTICLE

Combined Butalbital/Acetaminophen/Caffeine Overdose: Case Files of the Robert Wood Johnson Medical School Toxicology Service

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Case Presentation

A 40-year-old woman with no previous medical problems presented to the Emergency Department (ED) 2 h after ingesting an unknown amount of Fioricet® (butalbital/acetaminophen/caffeine), oxycodone, and fentanyl patches about 90 min prior to emergency medical service (EMS) dispatch. The patient's husband reported they had had a fight, and he went down to the basement; when he came back upstairs, he found the patient unconscious with an empty pill bottle. A call to the patient's pharmacy by ED staff revealed that the patient had her prescription for butalbital/acetaminophen/caffeine tablets refilled 5 days earlier and that she had convinced the pharmacist to override the refill amount to dispense 540 tablets; according to the pharmacist, the patient stated she was going on a trip to Italy and needed a 6-month supply. EMS personnel removed a fentanyl patch (unknown strength) from her skin. The source of the fentanyl and the strength and formulation of the oxycodone were not recorded. Prehospital treatment included naloxone 4 mg IV without any noticeable clinical response, insertion of a nasal trumpet, and initiation of bag-valve-mask ventilation. A fingerstick glucose was 137 mg/dL.

On arrival to the ED, the patient was unconscious with the following vital signs: blood pressure, 98/54 mmHg; pulse, 72 beats/min; respiratory rate, 14 breaths/min; and pulse oximetry, 100 % on a non-rebreather mask. Auscultation of her chest revealed clear but bilaterally diminished breath sounds and a regular cardiac rhythm without murmurs, rubs, or gallops. The patient's ventilation improved with jaw thrust, but, due to increased secretions, she was intubated within 10 min of ED arrival using etomidate and succinylcholine.

On further examination, she had palpable distal pulses, and her abdomen was soft and non-tender. The patient's pupils were 1–2 mm in diameter and sluggishly reactive to light. The patient was noted to be shivering prior to being fully exposed, and her skin was warm and dry, revealing no signs of traumatic injuries.

An ECG revealed a normal sinus rhythm at 86 beats per minute with a prolonged QTc interval (504 ms). An orogastric tube and Foley catheter were both inserted, with a large volume (700 cc) of dark-colored urine quickly filling the Foley bag. Activated charcoal 50 g was administered via orogastric tube. Due to the reported large ingestion of acetaminophen and some initial uncertainty about the time of ingestion, an IV *N*-acetylcysteine (NAC) infusion was started according to the 21-h protocol, prior to obtaining serum acetaminophen level results. About 90 min after arrival (3 h after ingestion), the patient began having massive diuresis, producing 5,800 cc of urine over 1 h. Due to concerns about the patient's reported fentanyl patch ingestion and the lack of knowledge regarding possible extended-

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release formulations, whole bowel irrigation with polyethylene glycol-balanced electrolyte solution was also initiated.

What Is "Fioricet®"

Fioricet® (Watson Laboratories, Inc) is a combination tablet consisting of 40 mg of caffeine (1,3,7–trimethylxanthine), 325 mg of acetaminophen, and 50 mg of butalbital (5-allyl-5-isopropylbarbituric acid). Fioricet® is primarily intended as treatment for tension headaches [1].

Caffeine is a methylxanthine similar to theophylline and theobromine. While caffeine is used for stimulant and mood-elevating effects in drinks such as coffee, it also has been used to treat neonatal apnea and headaches in combination with other analgesics. Theophylline has classically been used to treat bronchospastic airway diseases such as asthma and COPD, although it has generally fallen out of favor to pure β-adrenergic agonists due to their better safety profiles [2]. As a group, methylxanthines cause the release of catecholamines, which subsequently stimulate β_1 and β_2 receptors, accounting for their stimulant effects. Methylxanthines' role in treating bronchospastic disease is due to both bronchodilatory and anti-inflammatory mechanisms. Toxic concentrations of caffeine (such as those achieved with oral doses >1 g) inhibit phosphodiesterase and thus increase levels of cAMP, promoting central nervous system (CNS) excitation, peripheral vasodilation, myocardial stimulation, and smooth muscle relaxation [3]. In addition, methylxanthines antagonize the benzodiazepine receptor, which likely contributes to the refractoriness of seizures from toxicity from these agents.

Acetaminophen, the second ingredient in Fioricet®, inhibits the synthesis of prostaglandins and hypothalamic heat regulation in the CNS and blocks peripheral pain impulses. Finally, butalbital is a short-to-intermediate acting barbiturate. The effects of butalbital in isolation are not well understood, as it is only available in combination products. Barbiturates have muscle-relaxing and anti-anxiety properties. A reason for butalbital's use in conjunction with caffeine may be to antagonize the unwanted central stimulating effect of caffeine [4].

How Do Methylxanthines Cause Systemic Toxicity?

When ingested orally, caffeine has nearly 100 % bioavailability and produces peak plasma concentrations within 30–60 min following ingestion. The amount of caffeine in a cup of coffee varies by volume in the "cup," the strength and method of brewing, and the roasting of coffee beans; however, a typical 5-ounce (150 ml) cup of brewed coffee will contain around 85 mg caffeine [5]. Mean plasma caffeine concentrations reach around 12 mg/L after ingesting 250 mg of caffeine [6]. Toxicity is generally associated with plasma concentrations>30 mg/L [3, 6, 7]. While the fatal oral dose of caffeine is likely around 10 g, the highest reported ingestion to have been survived is 24 g, (plasma concentration, 200 mg/L) [7, 8]. Death has been reported from intravenous injection of 3.2 g of caffeine [9]. Methylxanthine toxicity causes nausea, vomiting, mental status changes, seizures, hypotension, and dysrhythmias. Ingestions involving combination tablets with butalbital can additionally induce respiratory depression, thus, gaining early control of a patient's airway is a priority.

Toxicity within the gastrointestinal tract can cause nausea and vomiting. Emesis is often the most predominant symptom, occurring in 71–100 % of acute intoxications and may be difficult to control [10–12, 42]. Furthermore, methylxanthines promote gastric acid secretion, and their smooth muscle relaxing effects contribute to both gastritis and esophagitis, as seen with chronic use [13, 34].

Multiple mechanisms have been suggested for the arrhythmogenic capability of methylxanthines. Caffeine has been shown to cause a strong release of circulating catecholamines from the adrenal medulla, predominantly epinephrine [3, 14, 34]. Catecholamines stimulate the β_1 adrenoreceptor, augmenting the production of cyclic adenosine monophosphate (cAMP) by adenylate cyclase. Caffeine also can inhibit the degradation of cAMP by phosphodiesterase, further augmenting intracellular cAMP levels and inducing cardiac dysrhythmias [6, 15–17]. Additionally, caffeine induces calcium release from the sarcoplasmic reticulum into the cytosol and then quickly inhibits calcium's re-uptake back into the sarcoplasmic reticulum. The increased calcium concentrations may then provoke dysrhythmias [17–21]. Finally, caffeine may induce dysrhythmias by blocking cardiac adenosine A_2 receptors, whose action has been shown to be antiarrhythmic [22]. Increased calcium concentration within muscles causes greater contractility and contributes to tremor, a common side effect. This, along with increased muscular activity during methylxanthine-induced seizures, may lead to rhabdomyolysis [23].

The hypotension that may be seen following methylxanthine overdose is believed to have two mechanisms. First, methylxanthines induce tachydysrhythmias. The increase in heart rate leads to inadequate filling of the heart, ultimately leading to a drop in cardiac output. Second, increased circulating catecholamines stimulate β_2 adrenoreceptors in vascular smooth muscle, resulting in vasodilation and hypotension [3, 24, 25]. By carrying additional methyl groups, caffeine has greater CNS penetration relative to other methylxanthines and has been able to cause prolonged seizures [24, 62]. Under normal conditions, adenosine receptor A_1 stimulation is responsible in terminating seizure activity. Likewise, stimulation of adenosine receptor A_2 enhances blood flow to the brain during seizures via cerebral

vasodilatation. During methylxanthine intoxication, the increased metabolic demand from seizures may not be met by an increase in cerebral blood flow, due to vasoconstriction, allowing hypoxia to contribute to prolonged seizures [24, 62]. Furthermore, caffeine has been found to be a competitive antagonist of benzodiazepines at the benzodiazepine receptor and may contribute to the seizures' intractability [3]. Caffeine has been documented to cause anxiety, confusion, and delirium as well [30].

Caffeine toxicity may be accompanied by hypokalemia, hypomagnesemia, and hypophosphatemia [8, 31]. Hypokalemia is the most frequent electrolyte derangement reported, occurring to some degree in almost all cases of acute methylxanthine overdose [32, 33]. Prolonged β_2 adrenergic agonism from high circulating concentrations of catecholamines, particularly epinephrine, will result in a shift of serum potassium into the intracellular compartment, while keeping total body stores normal [3, 8, 32, 34]. Likewise, aminophylline infusions cause elevations in plasma insulin levels, which may exacerbate this derangement [35, 36]. While gastrointestinal losses could be another contributing cause, hypokalemia has been shown to precede emesis and has occurred in cases without emesis [33]. Vomiting may, however, contribute to ongoing fluid losses. Hyperglycemia, hyperinsulinemia, leukocytosis, metabolic acidosis, and ketosis have also been reported [3, 8]. Elevated levels of cAMP presumably via both increased catecholamines and phosphodiesterase inhibition have been shown to stimulate hepatic glucose production and pancreatic insulin release [32, 37, 38]. High levels of both epinephrine and norepinephrine may lead to lactic acidosis by compromising peripheral tissue oxygen supply via vasoconstriction and reducing hepatic clearance of lactate through changes in hepatic blood flow [31, 39, 40].

Case Continuation

The initial set of laboratory values was significant for a metabolic acidosis with hypokalemia (Table 1). The patient began to have a seizure about 1 h after arrival, and she was treated with 2 mg IV lorazepam, then another 4 mg lorazepam with control of the seizures, and then sedated with a propofol infusion at 30 mcg/kg/min. The patient's rectal temperature was noted to be 34.4 °C, and she was treated with warm IV fluids and a forced warm-air blanket. The serum acetaminophen level was 153.8 μg/mL (normal, 10–30 μg/mL), ethyl alcohol was <5.0 mg/dL, and the salicylate level was <4.0 mg/dL. A routine urine drug screen was positive for barbiturates and negative for benzodiazepines, cocaine, opiates, and tetrahydrocannabinol. The patient's subsequent 2-h urine output was 6 L, which was matched by IV fluid volume administration. Given the patient's critical clinical condition, and without a readily available caffeine assay, a hemodialysis catheter was inserted for emergent dialysis due to presumed severe caffeine toxicity.

Table 1 Laboratory test results

Test	Result	Reference value
White blood cell count (WBC)	9.4 k/μL	4–10.5 k/μL
Hemoglobin (Hg)	13.9 g/dL	12–15 g/dL
Hematocrit (Hct)	41.8 %	36–46 %
Platelets	288 k/μL	150–400 k/μL
Sodium (Na)	133 mEq/L	135–145 mEq/L
Potassium (K)	2.6 mEq/L	3.5–5 mEq/L
Chloride (Cl)	108 mEq/L	96–112 mEq/L
Bicarbonate (HCO_3)	19.1 mEq/L	24–32 mEq/L
Blood urea nitrogen (BUN)	19 mg/dL	6–23 mg/dL
Creatinine (Cr)	0.7 mg/dL	0.4–1.2 mg/dL
Glucose	133 mg/dL	70–100 mg/dL
Calcium (Ca)	8.9 mg/dL	0.6–10.4 mg/dL
Anion gap	12.9 mEq/L	7–15 mEq/L
Protein	7.1 g/dL	6–8 g/dL
Albumin	4.3 g/dL	3.5–5.5 g/dL
Bilirubin, total	0.7 mg/dL	0.1–1.2 mg/dL
Alkaline phosphatase	59 IU/L	37–107 IU/L
Alanine aminotransferase (ALT)	21 IU/L	3–40 IU/L
Aspartate aminotransferase (AST)	22 IU/L	12–45 IU/L
Magnesium	1.6 mg/dL	1.8–2.5 mg/dL
Lactate	3.2 mmol/L	0.5–2.2 mmol/L
CPK	121 IU/L	25–150 IU/L
CKMB	[Not performed]	0.0–6.3 ng/mL
Troponin I	<0.01 ng/mL	0.00–0.50 ng/mL
pH	7.21	7.36–7.42
pCO_2	34 mmHg	25–45 mmHg
Total CO_2	14.0 mEq/L	24–32 mEq/L
$p0_2$	121 mmHg	80–115 mmHg
0_2 Saturation	96.9 % (FiO_2=100 %)	94–100 %

Is Hemoperfusion Still a Viable Alternative to Modern-Day Hemodialysis?

Caffeine is primarily metabolized via demethylation by CYP 1A2, with plasma protein binding of 36 % and a volume of distribution of 0.5 L/kg [24, 41]. Because of its low volume of distribution, caffeine is amenable to extracorporeal methods of elimination. Charcoal hemoperfusion has traditionally been regarded as the method of choice for enhanced elimination of methylxanthines, particularly theophylline [42, 43]. While the endogenous rate of theophylline

clearance has been demonstrated to be approximately 50 mL/min, hemoperfusion derived rates have been reported up to four to six times higher [42, 44, 45]. Hemodialysis, while used, has historically had substantially lower clearance rates (around 100 mL/min) compared with hemoperfusion [43, 46–49].

Nonetheless, advances in modern-day hemodialysis now allow for much greater flow rates (as high as 300 mL/min) and a potential increase in methylxanthine clearance. Furthermore, hemodialysis offers additional advantages such as correcting electrolyte derangements and fluid balance, both of which are common issues in methylxanthine toxicity. Hemodialysis also has a better safety profile in comparison to hemoperfusion. In a study of those undergoing hemoperfusion for theophylline toxicity, complication rates of 18 % have been observed, involving bleeding diatheses, thrombocytopenia, and hypocalcemia, versus 0 % with hemodialysis [42]. This study failed to demonstrate a significant clinical advantage of hemoperfusion over hemodialysis, while both methods had comparable reductions in morbidity and mortality [42]. Because hemodialysis equipment and trained personnel are more readily available, hemoperfusion has fallen out of favor as an enhanced elimination modality.

Another limitation to hemoperfusion is cartridge saturation. While the initial drug extraction efficacy of each charcoal hemoperfusion cartridge begins near 100 %, it drops close to 65 % after 90 min of use, becoming less efficient than hemodialysis. As a result, single-use cartridges need to be replaced about every 2 h to maintain efficacy of the treatment [44, 50]. In an effort to slow the rate of cartridge saturation, modalities such as serial hemodialysis and hemoperfusion have been employed. By utilizing this method, extraction efficacy greater than 94 % at 60 min has been reported [50]. The use of both modalities in tandem thus offers not only enhanced clearance but also correction of electrolyte imbalances, and prolongs the life of the charcoal hemoperfusion cartridge and has been shown to offer advantages to either method alone.

What Are the Indications for Hemodialysis or Hemoperfusion for Methylxanthine Toxicity?

Most guidelines developed for enhanced elimination of methylxanthines have primarily focused on theophylline. The therapeutic serum concentration of theophylline is between 10 and 20 μg/mL. It has a narrow therapeutic window, with >75 % of patients exhibiting adverse reactions with levels greater than 25 μg/mL [51]. The risk of side effects increases with higher theophylline concentrations, and the majority of seizures occur in patients with concentrations greater than 40 μg/mL [52–54]. Further reports suggest that peak serum theophylline concentrations were a predictor of toxicity [55–57]. Even so, no consensus guidelines existed for when to employ hemoperfusion, with threshold serum theophylline levels ranging from 330 (59.4) to 550 μmol/L (99 μg/mL) [10, 58, 59]. Recommendations made by Park et al. and revised by Goldberg et al. suggest that hemoperfusion be performed in patients with a serum theophylline concentration greater than 80 μg/mL following an acute intoxication and in those with a serum level greater than 60 μg/mL with a chronic ingestion. They further suggested that those who could not tolerate oral charcoal were older than 60 years of age or had concurrent heart and liver dysfunction were at increased risk [58–61]. Extracorporeal elimination should be begun prior to onset of major toxicity involving seizures or dysrhythmias, since once these complications are present the use of enhanced elimination has not been shown to terminate such events [42].

While the toxicity from other methylxanthines, such as caffeine, should be managed in a similar manner, quantitative caffeine levels are less commonly available than theophylline levels in an acute setting. Nonetheless, with massive caffeine ingestions, a considerable amount of caffeine may be metabolized to theophylline, resulting in detectable, and in some cases, nearly toxic, theophylline levels [8]. With caffeine overdose, obtaining a theophylline level may at the least confirm the class of ingestant and help guide management. In general, in the treatment of systemic toxicity, the patient's clinical picture (e.g., persistent seizures, cardiac dysrhythmias, hemodynamic instability) is the most important factor when deciding whether to utilize enhanced methods of elimination.

Case Continuation

The patient was transferred from the ED to the medical intensive care unit (MICU) where she continued to have large volume diuresis while concurrently undergoing emergent hemodialysis. At the completion of dialysis, the patient was given an additional loading dose of *N*-acetylcysteine over 1 h and then subsequent doses as per the 21-h NAC protocol. As the patient's urine output over the next 6 h was as high as 1,200 mL/hr, the MICU resident ordered administration of desmopressin 1 μg. During the subsequent 6 h, the patient's urine output dropped to an average of 550 mL/h. Potassium and magnesium were supplemented, and serum concentrations normalized. The patient was extubated the following morning.

The initial pre-dialysis caffeine level result was 51.2 μg/mL with a repeat the following morning (after dialysis) of 4.1 μg/mL. The patient ultimately admitted to ingesting around 100 tablets of Fioricet® in addition to her daily dose of oxycodone but denied ingesting any fentanyl patches. She had stated her intent was for recreational and "escape" purposes, rather than suicidal intent. The patient was

transferred out of the MICU, was seen by psychiatry, and was ultimately discharged 3 days post-ingestion without any noted neurologic sequelae.

What is the Role of *N*-acetylcysteine (NAC) in Patients Being Dialyzed for Another Indication? Does NAC Get Dialyzed Away?

N-Acetylcysteine has long been used in the treatment of acetaminophen overdose. Its main efficacy comes in its ability to stimulate glutathione synthesis [62]. By repleting glutathione, NAC works to prevent the binding of *N*-acetyl-p-benzoquinoneimine to hepatocytes with subsequent necrosis. In this case, as the patient's time of ingestion was unknown, she was promptly given the standard 150 mg/kg loading dose of NAC. However, when the patient underwent dialysis for caffeine toxicity, it was not clear what would happen to the NAC that had already been infused, and therefore whether the patient required a repeat NAC loading dose or not.

NAC has a volume of distribution of about 0.5 L/kg, is about 83 % protein-bound, and has a mean half-life of about 6 h. 70 % of its total body clearance is non-renal [63–65]. While it has a relatively small volume of distribution, the high protein-bound percentage of NAC makes it unclear whether it can readily cross a dialysis membrane. In patients with renal insufficiency undergoing hemodialysis, it has been reported that about half of NAC given during dialysis should be replaced. In instances where such patients have concurrent acetaminophen poisoning, it has been recommended that they receive a supplemental dose of NAC at the end of their dialysis session [66]. To the best of our knowledge, there are no reports directly measuring NAC concentrations in otherwise healthy individuals subsequently undergoing hemodialysis. As a result, we elected to give our patient a supplemental loading dose of IV NAC following hemodialysis.

What Is the Role of Vasopressin or DDAVP in Caffeine Toxicity?

Vasopressin possesses many properties that can counteract effects seen with caffeine toxicity. Arginine-vasopressin (AVP) is endogenously released from the posterior pituitary gland in response to reduced plasma volume or increased serum osmolality and is most commonly regarded to as the anti-diuretic hormone [67]. Under normal conditions, its major role is in the regulation of water balance. Vasopressin has affinity for V_1 (vascular) and V_2 (renal) receptors. V_1 receptors are present on vascular smooth muscle. Their stimulation induces phosphatidylinositol turnover and mediates vasoconstriction by releasing calcium from intracellular stores [24, 68–70]. This directly inhibits the adenylate cyclase-mediated vasodilation caused by caffeine. Not surprisingly, the use of intravenous vasopressin as a pressor agent in massive caffeine overdose has been described [24]. Conversely, while being a potent vasoconstrictor in skin and skeletal muscle, vasopressin has been shown to produce vasodilation in renal, pulmonary, mesenteric, and cerebral circulations. This is most likely due to endothelial NO release [71–75]. Vasopressin-induced cerebral dilation may work to oppose caffeine (A_2 blockade) induced vasoconstriction.

Vasopressin V_2 receptors are present in renal endothelial cells and the collecting duct system. Their stimulation results in a rise in cAMP via activation of adenylate cyclase [69, 76, 77]. Rising cAMP levels cause an increase in water permeability of the apical membrane and trigger the release of more water channels to appear on its surface. This results in increased reabsorption of water and concurrent decrease in urine output [76–80]. S1-Desamino-8-D-arginine vasopressin (DDAVP), or desmopressin, is a synthetic vasopressin with antidiuretic properties and little to no vasopressor effect [81]. Desmopressin has affinity for the V_2 receptor 1.6 times that of AVP [82]. Thus, DDAVP administration may have benefit in counteracting caffeine-induced diuresis. In our patient, urine output dropped 50 % following a 1 μg desmopressin dose.

What Is the Role of β Blockers in Methylxanthine Toxicity?

Hypotension is a common complication in methylxanthine toxicity. This effect is primarily due to β_1 receptor-mediated tachydysrhythmias and β_2-receptor-mediated vascular smooth muscle vasodilation [3, 24, 25]. Treatment of such hypotension has the possibility of being refractory to IV fluids and standard vasopressor therapy [83]. Consequently, the use of nonselective β-blockers such as propranolol has been used in theophylline toxicity [84–86]. By blocking β_1-stimulated tachycardia, propranolol is able to increase end diastolic filling and subsequently, blood pressure. At the same time, propranolol has been observed to improve blood pressure in patients with persistent tachycardia, suggesting the probable importance of its ability also to block β_2-mediated vasodilation. Propranolol is also able to counteract catecholamine-induced tachydysrhythmias, tremor, and agitation—all of which are likely to occur in caffeine toxicity [87]. While successful in their ability to ameliorate the toxic effects of caffeine, the safety of nonselective β-blockers has been questioned in patients with asthma or chronic obstructive pulmonary disease [85–87]. The use of β_1-selective β blockers such as esmolol has been described.

With a half-life of 9 min, esmolol is a short-acting β_1-selective β blocker [88]. Its main benefit is thought to be inhibition of β_1 cardiac receptors, blocking catecholamine-induced tachycardia. At doses adequate to produce β_1

blockade, there has been no noticeable effect on β_2 receptors. Not surprisingly, esmolol has been safely used in patients with asthma [89, 90]. Esmolol offers the advantage of having a short duration of clinical effect, making it easily titratable. No significant persistent drug effects have been evident 30 min following its discontinuation [91]. Nevertheless, it has been reported that continued treatment (>1 h) with β-blocking agents such as esmolol for persistent tachycardia can cause a decrease in cardiac index and result in cardiogenic shock, although not all reports reached the same conclusion [86, 91]. As a result, the use of continuous hemodynamic monitoring should be stressed. Still, β blocker use in caffeine toxicity may restore hemodynamic stability in an otherwise unstable patient.

Was This Patient Relatively Protected from Methylxanthine Neurotoxicity by the Presence of Barbiturates (Butalbital) Found in the Fioricet®?

Methylxanthine-induced neurotoxicity is most manifestly evident by the presence of seizures occurring due to adenosine A_1 and A_2 receptor antagonism within the brain [24–29]. The mainstay of treatment for methylxanthine-induced seizures has been the use of benzodiazepines and barbiturates, with diazepam and phenobarbital frequently being described as effective agents [54, 92]. In fact, diazepam, clonazepam, valproic acid, and phenobarbital have all been found to be of benefit in their ability to increase the CNS threshold for methylxanthine-induced, particularly theophylline-induced, seizures. In contrast, phenytoin had no such effect, and does not serve a role in treatment [92, 93]. The use of phenobarbital in theophylline-intoxicated rats has been described to prevent seizures and improve survival (from 20 % to 50 %) [92]. We hypothesize that the presence of butalbital within the Fioricet® may have exhibited a neuroprotective effect on our patient. While she did have a seizure, it was terminated by the use of modest doses of lorazepam without occurrence of further episodes. In addition, she made complete recovery to her baseline mental status. Nonetheless, it cannot be overlooked that use of propofol infusion may have served as a confounder.

Conflict of Interest We have no conflicts to report.

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