Outcomes After High-Concentration Peroxide Ingestions

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Study objective: In cases of high-concentration peroxide ingestion reported to US poison centers, we describe medical outcomes, examine the role of hyperbaric oxygen, and review the use of endoscopy.

Methods: The study was a retrospective analysis of a structured database, the National Poison Data System. The chart for each poison center case of a high-concentration (>10%) peroxide ingestion was obtained and abstracted in a standardized fashion; 1,054 cases were initially considered and 294 cases met inclusion criteria. The primary outcome of possible embolic event was defined as seizure, altered mental status, respiratory distress, hypoxia, hemodynamic instability, ECG changes, radiographic evidence of cerebrovascular accident, focal neurologic deficit on examination, pulmonary embolism, cardiac emboli, elevated troponin level, physician bedside diagnosis, or rapid improvement after hyperbaric oxygen therapy. Both descriptive statistics and logistic regression models were used to analyze the data.

Results: In the 10-year study period, 41 of 294 patients (13.9%; 95% confidence interval 10.2% to 18.4%) with symptoms after high-concentration peroxide ingestion demonstrated evidence of embolic events, and 20 of 294 (6.8%; 95% confidence interval 4.2% to 10.3%) either died or exhibited continued disability when the poison center chart was closed. Improved outcomes were demonstrated after early hyperbaric oxygen therapy. Endoscopy revealed grade 3 or 4 lesions in only 5 cases.

Conclusion: Symptomatic high-concentration peroxide exposures had a high incidence of associated embolic events in this cohort. Patients with evidence of embolic events had a high rate of death. Early hyperbaric oxygen therapy may be useful, but routine endoscopy is unlikely to be of benefit. [Ann Emerg Med. 2017;69:726-736.]

Please see page 727 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Hydrogen peroxide is a colorless, odorless liquid typically encountered at household concentrations of 3% to 5%. It is a weak acid (pK_A 11.75) and a strong oxidizer. At this strength, it is commonly used for wound irrigation, hair treatment, and other cosmetic purposes. Household-concentration peroxide is widely acknowledged as safe, with the rare case of harm after massive ingestion or irrigation under pressure.

In contrast, a much greater danger is posed by exposures to high-concentration peroxide (>10%). Peroxide at this concentration is most often encountered in commercial settings, stored in bulk for dilution to household strength often with a label of "food grade hydrogen peroxide," or as part of complementary or alternative medicine therapy. In the latter indication, small amounts are diluted to "hyperoxygenate" the body.

Few in the medical community are aware of the dangers associated with exposure to this product. On contact with tissue, 1 mL of 35% hydrogen peroxide rapidly releases approximately 100 mL of oxygen.[1] The strong oxidizing properties of hydrogen peroxide and sudden volume of oxygen released in high-concentration ingestions have resulted in multiple case reports of harm in users. The proposed mechanisms of toxicity include gas embolism, caustic injury, and direct cytotoxic effects. It is presumed that local injury to the gut vascular wall and massive concentration gradients allow entry into the circulatory system. In the majority of cases, radiography demonstrates large amounts of gas in the portal system, associated with abdominal pain and nausea. However, in some cases, suspected arterial embolic effects have been observed. These include focal neurologic deficits suggestive of cerebrovascular accident; tachycardia, hypotension, and

Editor's Capsule Summary

What is already known on this topic

High-concentration hydrogen peroxide exposures are toxic.

What question this study addressed

What are the effects of high-concentration hydrogen peroxide exposures in humans?

What this study adds to our knowledge

In a retrospective national poison database analysis reviewing all symptomatic high-concentration peroxide exposures during a 10-year period, a high incidence of embolic events and permanent disability or death occurred among 294 symptomatic patients. Early hyperbaric oxygen therapy may decrease the risk of subsequent embolic events. Clinically important caustic injury was rare.

How this is relevant to clinical practice

After this exposure, patients should be monitored for embolic events. Routine endoscopy for caustic lesions is not warranted.

dyspnea consistent with pulmonary embolism; and hypotension and elevated troponin level consistent with cardiac emboli.[1-8] Unfortunately, the current body of literature is limited to case series and case reports. Therefore, the spectrum of disease, commonness of severe outcomes, and potential benefits of interventions have not been studied in a systematic fashion.

In some cases, hyperbaric oxygen therapy has been used to reduce bubble size or enhance reabsorption of gas bubbles in the bloodstream, with various degrees of success.[9] Hyperbaric oxygen may also be used in an attempt to prevent delayed or persistent sequelae from ischemic perfusion injury. The largest case series to date documented 11 patients at a single site.[6] At this center, an aggressive protocol of early computed tomography (CT) and hyperbaric oxygen therapy was used in cases of portal venous gas even without other embolic signs and symptoms. It is unclear whether this protocol improved outcomes compared with those at other centers because no single center encounters sufficient cases for comparative analysis.

Additional injuries that may require intervention include caustic effects. Given the reliable presence of abdominal discomfort and frequent presence of scant hematemesis, endoscopy is often performed. However, there has been no systemic analysis of the necessity of endoscopy in cases of peroxide exposure. Furthermore, the relationship between embolic events and caustic injury is also not certain.

Consequently, there is limited evidence to inform diagnostic or therapeutic decisionmaking in regard to high-concentration peroxide ingestions. Theoretical and mechanistic rationales have driven previous recommendations, but the optimal management strategy has not been examined, to our knowledge.

Importance

High-concentration peroxide ingestions have been associated with embolic events in previous case reports and case series. However, the epidemiology, diagnostic and treatment variation, and outcomes related to such exposures have not been systematically studied because of the rare nature of the exposure—294 cases reported during 10 years to all US poison centers in this study—preventing a single center from performing an analysis of high-concentration peroxide ingestions. Furthermore, many cases result in serious disability or death.

Goals of This Investigation

In cases of high-concentration peroxide ingestions reported to US poison centers, our goal is to describe medical outcomes, examine the role of hyperbaric oxygen, and review the use of endoscopy after exposure.

MATERIALS AND METHODS

Study Design

The study is a retrospective analysis of a structured database, the National Poison Data System (NPDS) of the American Association of Poison Control Centers (AAPCC). The NPDS database contains all cases collected by US poison centers, with all centers using a standard format. Major fields are required before a case can be closed, ensuring complete reporting for significant events. However, data available through NPDS are limited in detail aside from required fields. Thus, the original chart for each poison center case was also requested from the original center and abstracted in a standardized fashion to obtain study-specific details missing from NPDS. Poison center documentation standards beyond NPDS minimum requirements vary greatly both between centers and from case to case. Consequently, there was incomplete ascertainment of many of the variables that were not NPDS required fields.

Selection of Participants

The NPDS database was queried for ingestions from 2001 to 2011 coded as a peroxide product with a concentration greater than 10% (see Appendix E1, available online at http://www.annemergmed.com, for individual product codes), with hyperbaric oxygen as a treatment (AAPCC generic code 143320 and hyperbaric oxygen as treatment), or with an outcome of moderate effects, major effects, or death (AAPCC generic code 143320 with corresponding outcome).

This search was intentionally broad to ensure capture of all potential cases, returning 1,054 records. Within the toxicology community, household-concentration peroxide ingestions are considered benign, with the possible exception of massive ingestion, vascular injection, or pressure irrigation of an open wound. Consequently, we believed that combining symptomatic low-concentration peroxide exposures with high-concentration ones, which are typically considered separate but related disease processes, was inappropriate. Thus, we limited analysis to high-concentration peroxide exposures. In addition, exposures reported to poison centers are often uncertain in nature or are not correctly identified. Given that true high-concentration exposures are reliably symptomatic, with a minimum of abdominal pain, oropharyngeal pain, or vomiting in previous reports, the cohort was limited to symptomatic exposures to avoid incorrectly labeled exposures.

Details on each case were requested from the original poison center. Redacted case notes were obtained from all 57 open and 3 of 6 closed poison centers. There were 18 missing records from the nonreporting closed centers. Participating poison centers excluded 358 cases because the peroxide concentration was found to be household strength (less than or equal to 10%) on review of the case at the site before transmission to the investigators. Two medical toxicologists served as trained reviewers, abstracting a total of 678 cases: 384 were excluded because of household-strength peroxide, noningestion exposure, or no symptoms (Figure), leaving 294 cases for inclusion. Only cases in which the peroxide concentration was explicitly noted to be greater than 10% (or described as food grade, industrial grade, or high concentration if the concentration was not quantitatively identified) and in which the patient had any signs or symptoms of toxicity, ranging from an episode of emesis to critical illness and death, were included in the analysis. All other peroxide cases were presumed household concentration.

Both toxicologists reviewed each included case. If there was disagreement, a third medical toxicologist also reviewed the case to adjudicate discrepancies. Sixty abstractions were analyzed to examine measures of agreement between reviewers. Interrater agreement was 92% between the 2 primary reviewers for all variables, combined with greater than 99% agreement for exclusion or inclusion of 10 key variables: possible or probable embolic effects, final outcome, age, amount ingested, concentration ingested, time to onset of embolic effects, CT of the abdomen findings, use of hyperbaric oxygen, time to initiation of hyperbaric oxygen, and endoscopy findings. Abstractors were not blind to study objectives. Variables were predefined. An Excel 2011 spreadsheet (Microsoft, Redmond, WA) with standardized variable coding was used by all reviewers. All statistical analysis was performed in

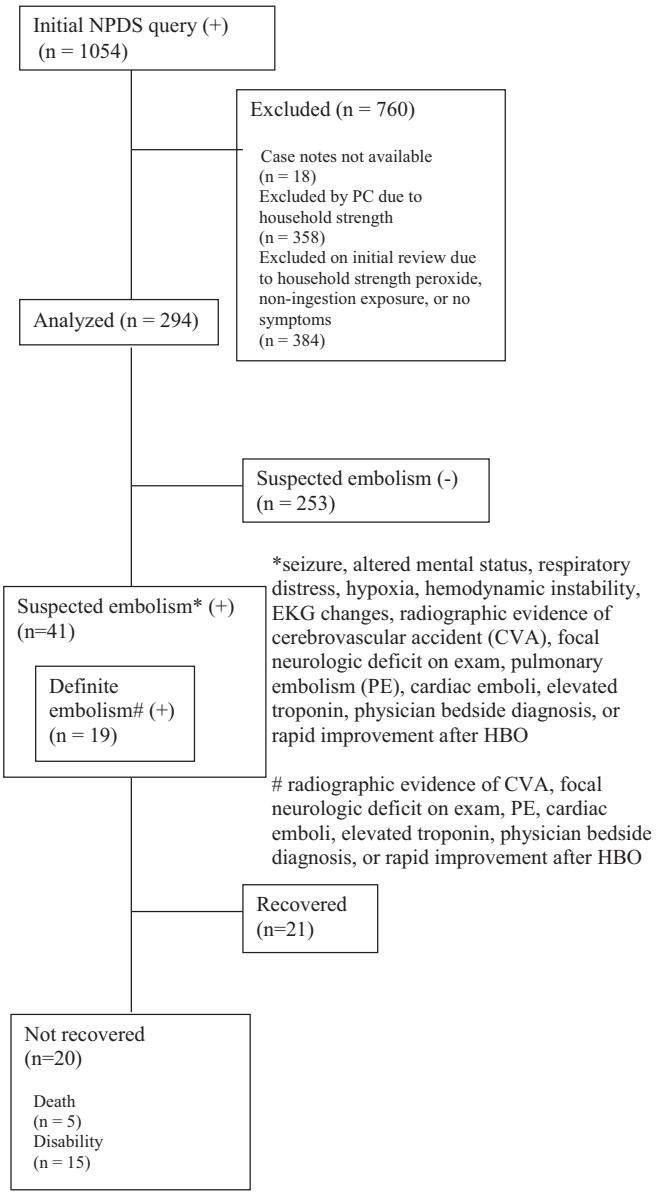

Figure. Enrollment. *PC*, Poison center; *HBO*, hyperbaric oxygen therapy.

Stata (version 11.2; StataCorp, College Station, TX). This study was approved by the local institutional review board.

Methods of Measurement

If not explicitly stated in the poison center chart, volume of ingestion was estimated at 15 mL for an adult swallow and 5 mL for a pediatric swallow.[10] Because many poison center charts provided incomplete data, only findings explicitly stated in the case notes were recorded, rather than making assumptions about missing data and introducing a large degree of uncertainty into the results. For purposes of developing a model, analysis was performed with only the variables as recorded and eliminating missing data. These results are reported. Alternative modeling assuming normal or negative values for missing data was also performed but did not change the variables of interest in the model. Consequently, the additional modeling was not reported.

Outcome Measures

Two hundred ninety-four cases were analyzed with a primary outcome of possible embolic event, defined as reported seizure, altered mental status, respiratory distress, hypoxia, hemodynamic instability, ECG changes, radiographic evidence of cerebrovascular accident, focal neurologic deficit on examination, pulmonary embolism, cardiac emboli, elevated troponin level, physician bedside diagnosis, or rapid improvement after hyperbaric oxygen therapy. Abstractors had to agree that the events were probably or definitely due to embolism after peroxide exposure versus an alternative cause for the case to be included in the primary analysis. A sensitivity analysis was performed that restricted the definition of embolic event to radiographic evidence of cerebrovascular accident, focal neurologic deficit on examination, pulmonary embolism, cardiac emboli, elevated troponin level, physician bedside diagnosis, or rapid improvement after hyperbaric oxygen therapy.

Primary Data Analysis

Analysis included descriptive statistics with 95% confidence interval (CI), P values calculated with χ^2 or Fisher's exact tests for categorical variables and t tests for continuous variables, and odds ratios (ORs) calculated with logistic regression. Given the lack of epidemiologic data or research beyond case series providing insight into predictors of embolism or outcome, we attempted to develop exploratory models using a large number of predictors of interest. Given the lack of a priori information surrounding the exposure, model development was performed in a stepwise fashion to ensure that potentially informative predictors were not prematurely discarded. Potential predictors identified in these models deserve additional study to determine their true predictive value. Multivariate logistic regression models were constructed with the Hosmer-Lemeshow main effects approach to identify predictors of embolic events. Univariate $P<.25$ was used as the threshold to enter the model, and predictors with a $P<0.1$ were retained. All statistical analysis was performed in Stata.

RESULTS

In the 10-year study period, 41 of 294 (13.9%; 95% CI 10.2% to 18.4%) symptomatic peroxide ingestion cases demonstrated evidence of a possible embolic event (Table 1). Under the more restrictive definition above, 19 of 294 patients (6.5%; 95% CI 3.9% to 9.9%) demonstrated evidence of an embolic event. A minimal number of cases involved coingestions (7/294; 2.4%); one of these involved a case of possible embolism but did not meet the more restrictive embolism definition. Patients met the following criteria for definite embolism: 8 of 19 radiographic evidence of cerebrovascular accident, 13 of 19 focal neurologic deficit, 0 of 19 pulmonary embolism, 1 of 19 cardiac emboli, 7 of 19 elevated troponin level, 11 of 19 physician bedside diagnosis, and 1 of 19 rapid improvement after hyperbaric oxygen therapy. None of the definite embolism cases were classified as such based solely on physician bedside diagnosis.

Final outcomes in many cases were severe, with 20 of 294 patients (6.8%; 95% CI 4.2% to 10.3%) either deceased or exhibiting continued disability when the poison center chart was closed. All 20 with an outcome of death or continued disability demonstrated evidence of embolic events. Median duration of follow-up before poison center case closure in those 15 cases of continued disability was 102 hours (range 48 to 384 hours). Death occurred in 5 of 294 symptomatic patients (1.7%; 95% CI 0.6% to 3.9%), including 5 of 41 (12.2%; 95% CI 4.1% to 26.2%) with evidence of possible embolic

Table 1. Characteristics.

Characteristics	Suspected Embolism (41)	Local Effects Only (253)
Age, mean, y	53.5	42.9
Sex, women, %	48.8	46.2
Intent, %		
Unintentional	63.4	80.6
Intentional, therapeutic	29.3	15.4
Intentional, self-harm	7.3	4.0
Estimated volume, median, mL	30	15
Peroxide concentration, %	35	35

Table 2. Death cases.

Age, Years/ Sex	Amount, mL	Conc, %	Intent	Sxs	Details
35/F	180	Unknown	Unknown (drank unlabeled bottle of high concentration H_2O_2 in refrigerator)	Emesis, AMS, tachycardia, decerebrate posturing, seizure, ventricular tachycardia, and herniation	Seizure at home and incapacitated for 1 h before presentation. Intubated on arrival. XR/CT without extraluminal gas. EGD with gastritis. Herniated in ICU.
82/F	30	35	Intentional: misuse (husband was "homeopath" and gave wife H_2O_2)	Emesis, possible aspiration, AMS, tachycardia	Intubated for decreased LOC/ emesis. Eventually extubated but minimally responsive. Comfort care only and then died in the ICU.
69/M	≤45	20–40	Unintentional (spouse saw patient take sip from unmarked bottle of H_2O_2 in refrigerator)	AMS, elevated troponin level	Intubated for decreased LOC. Facility declined HBO. Suspected basilar insult. Care withdrawn.
55/M	960	35 (diluted with unknown amount of water)	Intentional: misuse (drinking H_2O_2 regularly but visiting relatives and used unfamiliar preparation)	AMS, respiratory distress, emesis, tachycardia	Found obtunded 30 min after ingestion and intubated. Initial CT result negative. Repeated CT No. 1 with R frontal infarct and cerebral edema. Repeated CT No. 2 with multiple infarcts in pons, brainstem, cerebellum, and cerebral cortex. + Hemorrhagic transformation with midline shift. Extubated and received comfort care before dying.
73/M	15	35	Unintentional (took a "swig" from an unmarked bottle in refrigerator, thinking it was water)	AMS, emesis, tachycardia	Intubated for decreased LOC and emesis. HBO initiated 15 h after ingestion. Unresponsive when sedation stopped. Received comfort care and died in hospice.

Conc, Concentration; Sxs, symptoms; *H_2O_2*, hydrogen peroxide; *AMS*, altered mental status; *XR*, radiograph; *EGD*, esophagogastroduodenoscopy; *LOC*, level of consciousness.

events when the poison center was following the case (Table 2).

The time to onset of a possible embolic event varied greatly. Although determining accurate timing from poison center records is difficult, estimated time to onset of embolic symptoms ranged from immediate to 25 hours, with a median of 1 hour. The majority occurred quickly, with onset noted in 30 of 41 patients (73%) in less than 4 hours after ingestion.

However, in the other 11 cases, the first observation of a possible embolic event ranged from 7.5 to 25 hours after ingestion, suggesting that delayed onset of embolism is possible. Median time to onset in the 11 outliers was 10 hours, with 8 occurring between 7.5 and 12 hours. More than half of cases (6/11) met the restrictive criteria for definite embolism, with all 6 cases exhibiting possible or definite focal neurologic deficits. Evidence of embolism resolved in 7 cases. None of the patients died.

The case with longest time to onset, 25 hours, did not meet the restrictive criteria for definite embolism. The patient presented with normal vital signs and no neurologic deficit. He was then nonurgently intubated before esophagogastroduodenoscopy. Approximately 12 hours after esophagogastroduodenoscopy and 25 hours after presentation, the patient experienced a seizure, followed by another seizure 1.5 hours later. The patient was subsequently extubated. Neurology consultants suspected cerebral gas embolism as the cause of seizure activity but the patient declined imaging. The patient recovered fully without additional seizure activity.

A logistic regression model to identify predictors of an embolic event was built with variables eligible for model entry after univariate analysis or deemed biologically

relevant: age, sex, intent, peroxide diluted before ingestion, amount ingested, concentration, radiograph findings, and CT of the abdomen results (Table 3). Predictors of embolic events in the final model were age greater than 44 years (OR 2.5; 95% CI 1.1 to 5.9) and amount ingested in milliliters (OR 1.00; 95% CI 1.00 to 1.01). The point estimate for the latter OR was slightly greater than 1.00 but rounded to 1.00, and the lower bound of the CI was greater than 1. Unfortunately, no single finding was able to predict progression beyond local effects.

Of the 41 patients with concern for embolism, documented neurologic abnormalities such as altered mental status or decreased level of consciousness (35/41), focal neurologic deficit (15/41), and seizure (8/41) were most concerning, along with cardiopulmonary abnormalities such as tachycardia (16/41), hypotension (10/41), elevated troponin level (7/41), ECG abnormalities (6/41), respiratory distress (16/41), and hypoxia (12/41). Using only the 41 patients with evidence of embolic events, a logistic regression model to identify predictors of permanent disability or death was built with the variables eligible for model entry after univariate analysis or deemed biologically relevant: age, sex, intent, amount ingested, CT of the abdomen results, focal neurologic deficit, tachycardia, troponin-positive results, ECG result abnormal, pH, dyspnea, and time to embolic symptom onset (Table 4). Although the limited number of patients with embolic events resulted in wide CIs, predictors of permanent disability and death among patients with embolic symptoms were focal neurologic deficit (OR 10.7; 95% CI 1.8 to 62.3), age greater than 44 years (OR 6.44; 95% CI 0.8 to 50.0), and troponin level greater than 0.00 (OR 4.62; 95% CI 0.7 to 29.7).

Given the inability to identify patients at high risk for embolic events at initial presentation and the use of CT of the abdomen as a screening tool at some centers, the utility of CT of the abdomen to predict embolic events was examined. Six of 33 patients (18.2%; 95% CI 7.0% to 35.5%) with an initial CT demonstrating extraluminal air went on to experience an embolic event compared with 35 of 261 (13.4%; 95% CI 9.5% to 18.2%) of those with a negative or missing CT result. Of the 6 patients with portal gas on CT who exhibited evidence of embolism, 4 demonstrated embolic effects within an hour of exposure, 1 at 3.5 hours postexposure and another at 7.5 hours postexposure. Because some centers initiate hyperbaric oxygen therapy after a CT of the abdomen reveals extraluminal air and it is possible that early hyperbaric oxygen therapy prevents embolic events, we then examined only patients who did not receive hyperbaric oxygen therapy. Within this group, 3 of 14 (21.4%; 95% CI 4.7% to 50.8%) with extraluminal gas on a CT of the abdomen demonstrated evidence of an embolic event versus 31 of 226 (13.7%; 95% CI 9.5% to 18.9%) without a positive CT result. CIs were wide, although there appeared to be a greater proportion of patients with extraluminal gas on CT of the abdomen before development of an embolic event.

Table 3. Univariate predictors of embolic events.

Predictor	Number Analyzed	OR	95% CI
Dilution before ingestion	90	2.43	0.74–7.98
>44 y	284	2.47	1.18–5.16
Female sex	294	1.11	0.57–2.14
Intent	294		
Unintentional	230	1 [Reference]	1 [Reference]
Self-harm	6	1.57	0.18–13.96
Unknown	7	3.14	0.58–17.01
Therapeutic use	51	2.41	1.12–5.19
Amount, mL	249	1.00	1.00–1.01
Amount >15 mL	249	1.99	0.91–4.36
Conc, %	269	1.00	0.95–1.05
CT of the abdomen	45		
Negative	10	1 [Reference]	1 [Reference]
Gas in stomach wall	2	—*	—
Gas extending into portal system	31	0.29	0.06–1.41
Mesenteric vascular gas	2	—	—

*Dashes indicate data was unable to be calculated.

Table 4. Univariate predictors of permanent disability or death.

	OR	95% CI
>44 y	4.12	0.89–19.00
Sex, F	0.44	0.13–1.57
Intent		
Accidental	1 [Reference]	1 [Reference]
Self-harm	—*	—
Unknown	—	—
Misuse	1.50	0.52–8.51
Amount, mL	1.01	1.00–1.01
Concentration, %	0.98	0.87–1.11
CT A/P		
Negative	1 [Reference]	1 [Reference]
Gas in stomach wall	—	—
Gas extending into portal system	0.25	0.01–4.73
Mesenteric vascular gas	—	—
Focal neuro deficit	10	1.26–79.34
Tachycardia	3.00	0.68–13.31
Troponin level >0	4.85	0.86–27.22
ECG changes		
STEMI	—	—
Conduction disturbance	—	—
Dysrhythmia	—	—
Lowest pH	0.00	0.00–107.06
Dyspnea	1.62	0.41–6.34
Time to onset of embolic effects, h	1.07	0.96–1.20

STEMI, ST-elevation myocardial infarction.
*Dashes indicate data was unable to be calculated.

Use of hyperbaric oxygen therapy between centers varies widely. A limited number of centers recommend hyperbaric oxygen therapy to prevent occurrence of embolism after exposure to high-concentration peroxide, oftentimes recommending it after confirmation of extraluminal gas radiographically (typically portal venous gas on noncontrast abdominal CT). The use of hyperbaric oxygen therapy to prevent development of embolism was examined. One of 17 patients (5.9%; 95% CI 1.5% to 28.7%) who underwent hyperbaric oxygen therapy before embolic symptoms appeared, then developed embolic symptoms compared with 34 of 271 patients (12.6%; 95% CI 8.8% to 17.1%) who did not receive hyperbaric treatment. If we restrict the analysis to only patients who had a CT of the abdomen with extraluminal gas before embolic symptoms, 1 of 17 (5.9%; 95% CI 1.5% to 28.7%) who underwent hyperbaric oxygen therapy before embolic symptoms developed evidence of embolism at a later time compared with 3 of 14 (21.4%; 95% CI 4.7% to 50.8%) who did not undergo hyperbaric oxygen therapy. The one patient who developed symptoms concerning for an embolic event after initiation of hyperbaric oxygen therapy had a seizure during hyperbaric oxygen therapy. It was unclear whether this event was due to peroxide exposure or was treatment related, although the patient did exhibit altered mental status before hyperbaric oxygen therapy. This patient had complete resolution of symptoms.

Most poison centers recommend hyperbaric oxygen as treatment for gas embolism associated with high-concentration peroxide ingestion, although evidence supporting this therapy is limited to case reports of improvement and extrapolation from experience with dysbarism. The use of hyperbaric oxygen therapy after the development of embolic symptoms to prevent permanent disability or death was examined. Of patients who underwent hyperbaric oxygen therapy after developing embolic symptoms, 3 of 6 (50.0%; 95% CI 11.8% to 88.2%) died or had permanent disability compared with 17 of 33 (51.5%; 95% CI 33.5% to 69.2%) who did not undergo hyperbaric oxygen therapy. However, time to initiation of hyperbaric oxygen therapy may play a role. Hyperbaric oxygen therapy was initiated in the 3 patients who made a full recovery 4, 5.5, and 14 hours after ingestion compared with 14, 15, and 36 hours after ingestion in those who did not recover.

Given that concern for caustic injury is often a competing priority with possible embolism, the role of esophagogastroduodenoscopy in the management of these patients was also investigated. One hundred thirty of 294 patients (44.2%) underwent an esophagogastroduodenoscopy, with a median time to esophagogastroduodenoscopy of 15 hours postingestion. Esophagogastroduodenoscopy results were recorded in the poison center case notes for 118 patients. Only 3 of the 118 patients had a CT with extraluminal air. Injury grading as recorded by the treating team was as follows: 14 of 118 results (11.9%) were normal, 35 of 118 (29.7%) were grade 1 (mild irritation), 64 of 118 (54.2%) were grade 2 (superficial erosions/ulcerations), 3 of 118 (2.54%) were grade 3 (deep ulcerations), and 2 of 118 (1.69%) were grade 4 (necrosis). To summarize, only 5 of 118 patients (4.2%; 95% CI 1.4% to 9.6%) demonstrated deep ulcerations or necrosis (Table 5). One patient who underwent an esophagogastroduodenoscopy died, and the esophagogastroduodenoscopy did not reveal a grade 3 or 4 lesion in that case. All 5 patients with grade 3 or 4 lesions presented with vomiting, 4 of 5 (80%) reported hematemesis, and 4 of 5 (80%) experienced unintentional ingestions. Data from all patients with grade 3 or 4 findings would have been captured by restricting esophagogastroduodenoscopy to those with evidence of embolic event, significant gastrointestinal bleeding (melena or more than scant hematemesis), pneumomediastinum on radiography, or history of gastric bypass. There were 2 possible hollow viscous perforations (Table 5). Both were diagnosed as possible esophageal tears with definite pneumomediastinum by chest CT, although it was unclear whether the pneumomediastinum was due to a true perforation or gas released by peroxide. Neither patient required operative repair.

LIMITATIONS

The AAPCC (http://www.aapcc.org) acknowledges the following potential limitations with NPDS data: "AAPCC maintains the national database of information logged by the country's poison centers. Case records in this database are from self-reported contacts. They reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (eg, an ingestion, inhalation, or topical exposure, etc), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to poison centers and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s)." A discussion of these limitations has occurred in previous literature.[11]

Our specific results are limited by possible selection bias; more severe cases may be more likely to be reported to a

Table 5. Severe caustic injuries.

Age, Years/Sex	Amount, mL	Conc, %	Intent	Sxs	Details
Grade 3 or 4 lesions on esophagogastroduodenoscopy					
57/M	15	35	Unintentional (drank unlabeled water bottle full of H_2O_2 in refrigerator)	Emesis, AMS, possible oral edema, multiple seizures	Intubated for EGD. Esophagus with mild burns. Upper stomach with severe burns and "some blackening." Discharged without restrictions.
87/M	60	35	Unintentional	Emesis, sore throat, difficulty swallowing, elevated troponin level, and ST-segment elevation	Admitted to ICU. EGD with severe pharyngeal and gastric ulcerations. Moderate esophageal ulcerations. Marked pyloric stenosis. Began receiving steroids and PPI. Diet advanced and discharged without restrictions.
60/F	15	35	Unintentional (took "gulp" of unmarked liquid that she thought was water)	Vomiting, abdominal pain, melena, hypotension, anemia	Presented 2 days after ingestion. XR without free air. EGD with ulcers throughout. Ulcers "clipped" and "cauterized." Hct stable. Treated with PPI. Discharged, receiving soft mechanical diet.
42/F	15	35	Intentional: misuse (drinking H_2O_2 "to feel better" because she was told it would oxygenate her blood and give her energy)	Hematemesis, abdominal pain, anemia	History of gastric bypass 7 y before presentation. EGD with necrosis of jejunum. Treated with PPI. NPO on TPN at case closure.
Unknown age, adult M	240	35	Unintentional (inadvertently drank a "substantial amount" from bottle being kept in house for medicinal purposes; family believes it has healing antioxidant properties when taken orally)	Unable to swallow 1.5 h after ingestion. Hematemesis and abdominal pain.	Initial CT with pneumomediastinum and portal venous gas. EGD findings of duodenum irritated with black necrotic tissue. No oral or esophageal burns. Received TPN and PPI after EGD. Repeated CT with resolution of pneumomediastinum and portal venous gas. Diet advanced before discharge.
Possible perforation					
47/F	15	35	Unintentional (drank H_2O_2 from unlabeled container)	Emesis, throat irritation, diaphoresis	CT chest/abdomen with pneumomediastinum and possible esophageal tear. No EGD. Treated with dexamethasone, PPI, TPN, and antibiotics. NPO×1 wk and then diet advanced.
75/M	180	35 (25 drops of 35% H_2O_2 diluted in 180 mL of H_2O)	Intentional (drinks it daily for "health")	Emesis	CT chest/abdomen with pneumomediastinum and possible esophageal tear. EGD with gastritis, duodenitis, and esophagitis but no tear identified. NPO×1 wk and then diet advanced.

PPI, Proton-pump inhibitor; *Hct*, hematocrit; *NPO*, nil per os; *TPN*, total parenteral nutrition.

poison center, potentially overestimating the spectrum of disease. It is also true that the provider must recognize the possible connection between high-concentration peroxide ingestions and embolic events to report to the poison center. Therefore, we actually may have underestimated the true incidence of embolic events. In addition, poison center case notes are of variable quality. The estimates provided in this study either do not take into account missing data or presume they are normal. Thus, it is likely that patients have a greater burden of symptoms than reported here. Moreover, we depended on the poison center documentation of peroxide as the exposure of interest rather than an alternate substance incorrectly identified as peroxide. Nevertheless, description of the substances and case features were consistent with peroxide as the exposure. Finally, given the limited numbers available for analysis and resulting wide CIs, interpretation of the analysis must be tempered with an acknowledgement of the limitations of the data set. Additional discussion of limitations of the analysis is included in the discussion below.

DISCUSSION

The current human literature surrounding high-concentration peroxide ingestions is scant and limited to case reports and single case series. Recent case reports from the past 10 years range from cerebral embolism treated successfully[2,4] or unsuccessfully[7] with hyperbaric oxygen to portal venous gas observed without systemic embolism treated with[3,4,9] or observed without hyperbaric oxygen[5] to acute myocardial infarction with negative cardiac catheterization results.[8] The largest published case series represents the experience of a single center with an aggressive protocol calling for screening CT of the abdomen and immediate hyperbaric oxygen therapy for positive findings of portal gas.[6] Unfortunately, the current literature provides little direction in regard to prognosis, risk stratification, and treatment for the clinician faced with a symptomatic high-concentration peroxide ingestion.

Our results indicate that ingestion of small amounts, oftentimes a mouthful or two, of concentrated hydrogen peroxide led to critical illness caused by suspected embolism in 41 of 294 cases (13.9%) and severe long-term outcomes (death or continued disability) in 20 of 294 cases (6.8%) reported to US poison centers. In most cases, the patient swallowed the liquid unknowingly, mistaking it for water. The mean estimated volume of ingestion of 30 mL in patients with suspected emboli has been calculated to release 3 L of rapidly generated gas.[1] Such patients universally present with significant vomiting or abdominal pain unless systemic embolism has rendered them unresponsive.

Unfortunately, we were unable to determine risk factors that cause patients to develop systemic embolism. Demographic, history, and physical examination features performed poorly. Although more patients with intentional ingestions experienced an expected embolic event, this variable was not included in the final model. Given that 26 of 230 unintentional ingestions (11.3%) exhibited findings of embolism, all patients must be fully evaluated. Abdominal CT scanning without contrast, despite its expense and small risk of radiation exposure, is the primary option for initial imaging evaluation of patients with symptoms of vomiting, abdominal pain after exposure, or concern for embolism. However, few patients underwent initial abdominal CT scanning in this cohort. Although the wide CIs do not provide statistical certainty, the finding of extraluminal gas on CT of the abdomen may be a precursor to development of an embolic event. However, the true utility of noncontrast CT of the abdomen is unclear.

Although the majority of patients exhibited findings consistent with systemic embolism within 4 hours of ingestion, more than a quarter of patients ultimately found to experience suspected embolic effects developed progression beyond local findings after this period. The latest onset was 25 hours after exposure. Consequently, the typical 4- to 6-hour observation period after most toxic exposures appears inadequate for cases of symptomatic hydrogen peroxide exposure. Rather, even patients presenting only with gastrointestinal symptoms need to be observed in a setting with telemetry and hemodynamic monitoring, and while undergoing frequent repeated neurologic examinations.

Providers are then faced with a difficult decision involving the selection of patients who will appropriately benefit from transport for hyperbaric oxygen therapy with the presumed therapeutic mechanism of shrinking gas bubbles in the circulation. The risk of waiting for signs and symptoms of systemic embolism is that in some patients, gas will embolize past the liver to the heart, lungs, or brain.

Our study sheds light on what has been a divergent set of treatment strategies: "dive first" or "dive once symptomatic." Should clinicians wait until a neurologic deterioration occurs before hyperbaric therapy is performed? One strategy is admitting such patients to a level of care capable of initiating aggressive monitoring and performing hourly neurologic examinations. If utilizing this strategy, providers ideally should be able to rapidly access a hyperbaric unit if the patient develops signs or symptoms of embolism.

In centers where an aggressive "dive first" strategy has been adopted, portal venous gas resolves with a single course of hyperbaric oxygen therapy, presumably eliminating the need for further ICU admission, future

hyperbaric treatment, or imaging.[6] Consequently, there is a potential cost savings in addition to avoiding neurologic injury by using a protocol with CT and then hyperbaric oxygen therapy if the CT is positive for extraluminal gas. In this study, 254 patients did not receive hyperbaric oxygen therapy. Given that not all patients with initial symptoms will have a CT demonstrating the presence of portal gas, the number of potential additional patients in this cohort undergoing hyperbaric oxygen therapy would be somewhat less than 254. However, it is not clear whether portal gas is a necessary precursor to systemic embolism because an abnormal CT result in our study was not independently predictive of emboli.

In patients with portal gas on CT, those who were treated with hyperbaric oxygen had a lower rate of future embolic events (1/17 [5.9%] versus 3/14 [21.4%]). There appeared to be improved outcomes in patients treated with hyperbaric oxygen before onset of embolic phenomena, although CIs were wide, given the limited numbers of subjects available for analysis.

In patients who did not undergo hyperbaric oxygen treatment until evidence of embolism manifested, half (3/6) ultimately died or experienced permanent disability. This could imply a benefit for preemptive hyperbaric oxygen therapy or simply reflect a greater severity of disease in patients who underwent late hyperbaric oxygen treatment. Unfortunately, the rare nature of the exposure limits the number of cases available for analysis. In patients who underwent hyperbaric oxygen therapy after onset of systemic embolism, only those who received it at or before 14 hours after ingestion recovered fully. Consequently, hyperbaric oxygen therapy should be initiated as quickly as possible once neurologic symptoms occur. Thus, using a "dive once symptomatic" strategy will frequently necessitate transferring these patients to centers with hyperbaric oxygen therapy capability for observation to facilitate timely initiation of treatment if embolism occurs.

The final question facing many providers treating patients presenting after high-concentration hydrogen peroxide ingestion is perhaps better answered with our data. Upper gastrointestinal endoscopy is most likely to find significant lesions (grades 3 and 4) in patients exhibiting hematemesis, pneumomediastinum, or signs of other embolic phenomena. If signs of embolic phenomena exist, hyperbaric therapy should take precedence over esophagogastroduodenoscopy because the endoscopy is diagnostic and not therapeutic in these cases, and it is unlikely that routine endoscopy will be beneficial.

Last, this product is meant to be used by the dropperful, yet we encountered many case instances in which it was stored in a clear vessel in the refrigerator and appeared indistinguishable from water. As with many poison prevention efforts, keeping this product in its original container and adding both child-resistant capping and a colorizing agent may diminish accidental ingestion. A prospective cohort study determining the true incidence of critical illness and embolic events, as well as examining the role of early CT of the abdomen and hyperbaric oxygen therapy in cases of high-concentration peroxide ingestions, would be the ideal next step.

In conclusion, to our knowledge this study represents the first systematic investigation of high-concentration peroxide ingestions, furnishing valuable information to providers presented with such an exposure. First, it is clear that a large number of exposures result in critical illness, with continued disability or death in many of these cases. Consequently, early provider recognition of the potential severity is essential. Second, the benefit of hyperbaric oxygen either in preventing central embolism in patients exposed or in treating embolism once it occurs is still unclear. However, it is likely that hyperbaric oxygen therapy is most effective when performed early in the course. Finally, the routine use of endoscopy is unlikely to reveal significant caustic injury necessitating intervention. A more selective strategy may provide a higher yield of esophagogastroduodenoscopy in this population. This systematic investigation of high-concentration peroxide ingestions offers some clarity to the hazards posed by this transparent liquid.

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Author contributions: BWH, LKF, and BZH conceived the study and designed the trial. All authors supervised the conduct of the trial and data collection, undertook recruitment of participating centers and patients, and managed the data, including quality control. BWH analyzed the data, drafted the article, and made the primary response to editorial comments, with all authors contributing to and approving of said responses. All authors contributed substantially to article revision. BWH takes responsibility for the paper as a whole.

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IMAGES IN EMERGENCY MEDICINE

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DIAGNOSIS:

Neuroblastoma. This child presented with evidence of both Harlequin syndrome (unilateral loss of facial flushing and sweating, often exaggerated by physical activity)[1] and Horner's syndrome. Both findings suggested a right-sided lesion of the sympathetic pathway. Although acquired Horner's syndrome in a child may be idiopathic, other causes include compressive neoplasms (especially neuroblastoma), trauma, and carotid artery abnormalities.[2] Current recommendations are that a child with a new Horner's syndrome undergo MRI with and without contrast of the head, neck, and chest, as well as measurement of urinary catecholamine levels.[2,3]

Our patient was found to have metastatic disease. He underwent 18 months of treatment, including chemotherapy, tandem autologous stem cell transplants, radiotherapy, and immunotherapy, and is currently awaiting restaging studies.

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APPENDIX E1
High-concentration peroxide product codes

6241692	Biox H hatchery grade hydrogen peroxide	Biosentry	Clear liquid
5062726	Chemprox hydrogen peroxide, 27.5%	Atochem; Elf Atochem	Liquid
5062718	Chemprox hydrogen peroxide, 35%	Elf Atochem; Atochem	Liquid
5062768	Chemprox hydrogen peroxide, 35% Fg	Elf Atochem; Atochem	Liquid
5062701	Chemprox hydrogen peroxide, 50%	Elf Atochem; Atochem	Liquid
5062742	Chemprox hydrogen peroxide, 50% Ds	Elf Atochem; Atochem	Liquid
5062693	Chemprox hydrogen peroxide, 70%	Elf Atochem; Atochem	Liquid
5521342	Cupraetch (Tm) Me Additive	Atotech	Liquid
5067693	Cur 28	Elf Atochem; Atochem	Liquid
5088649	Cur No. 15	Elf Atochem; Atochem	Liquid
5823623	Cwc	Biolab	Clear liquid
4901933	Do All Oxygen Control Liquid	B-D Chemical	Liquid
2301531	Hi-Point D1, methyl ethyl ketone peroxide	Witco	
3173244	Hydrogen peroxide	Fisher Chemical	
3173252	Hydrogen peroxide	Fisons	
2919871	Hydrogen peroxide	Allied Chemical	
2973322	Hydrogen peroxide	Hach	
5508986	Hydrogen peroxide	Purepac Pharmaceutical	Liquid
5945328	Hydrogen peroxide	Helena Laboratories	Clear, colorless liquid
3093096	Hydrogen peroxide		
3132902	Hydrogen peroxide, 20%–40%	Fmc	Clear liquid
7276698	Hydrogen peroxide, 30%	Flinn Scientific	Clear liquid
3352038	Hydrogen peroxide, 40%–60%	Fmc	Clear liquid
3352088	Hydrogen peroxide, 8%–20%	Fmc	Clear liquid
3157248	Hydrogen peroxide, 30%	Fisher Chemical	
3157230	Hydrogen peroxide, 30%–35%	Fisher Chemical	
5062685	Hydrogen peroxide, 35%	Elf Atochem; Atochem	Liquid
5062677	Hydrogen peroxide, 50%	Elf Atochem; Atochem	Liquid
3157222	Hydrogen peroxide, 50%	Fisher Chemical	
6001559	Hydrogen peroxide Albone 35 N/R	Dupont, Canada Colors and Chemicals	Liquid
3029124	Hydrogen peroxide Lr tablets code 6454	Lamotte	Small tablet
5092856	Hydrogen peroxide solution	Safeway; Psp; R.W. Packaging	Liquid
7278785	Hydrogen peroxide solution, 2%–6%	Flinn Scientific	Clear liquid
5365120	Hydrogen peroxide solution, 3% 24062	Hach	Liquid
4812693	Hydrogen peroxide solution, 30% 144	Hach	Liquid
5342342	Hydrogen peroxide solution, 50% H_2O_2 21196	Hach	Liquid
4072031	Hydrogen peroxide solution with not less than 8% but less than 20% peroxide		
4072049	Hydrogen peroxide solution, with not less than 20% but not more than 52% peroxide		
3657397	Hydrogen peroxide solutions greater than 60%	Fmc	Clear liquid
3444918	Hydrogen peroxide solutions greater than 90%	Fmc	Clear liquid
6478998	Hydrogen peroxide topical solution	Vedco	Liquid
6518140	Hydrogen peroxide topical solution Usp	Vi-Jon Laboratories	Clear liquid
5342350	Hydrogen peroxide, 30% 24726	Hach	Liquid
5062750	Hydrogen peroxide, 50% Fg	Elf Atochem; Atochem	Liquid
5062669	Hydrogen peroxide, 70%	Elf Atochem; Atochem	Liquid
5062734	Hydrogen peroxide, 70% Ds	Elf Atochem; Atochem	Liquid
5062776	Hydrogen peroxide, 70% Mp	Elf Atochem; Atochem	Liquid
6269016	No Name Oxygen Cleaner	Capo Industries	Granular solid
5593409	Orajel Perioseptic Super Cleaning Mouth Rinse	Del Pharmaceuticals	Oral liquid
5404415	Oxee 100	Kay Chemical	Liquid
6273307	Oxy Boost	Hillyard Industries	Clear liquid
6128155	Perigel	Zila Pharmaceuticals	Gel/jelly
2272105	Peroxide	Procter & Gamble; Clairol	
2656449	Peroxide and plasticizer	Oatey	
4549212	Peroxide solutions	Revlon	
4549205	Peroxide solutions/hair lighteners	Revlon	
4068816	Peroxide, inorganic, n.o.s.		
6023149	Peroxides developers	Clairol	
6395150	Pro Tooth Whitening System: whitening gel	Natural White	Gel

Continued.

7101499	R.B.C.	Mt Hood Chemical	Clear liquid
6387438	Safetec hydrogen peroxide spray	Safetec of America	Clear liquid
4784545	Sc-590: Aluminum Desmut and Deodorizer	Novamax Technologies	
4784553	Sc-596: Aluminum Desmut Concentrate/use with sulfuric acid	Novamax Technologies	
4784579	Sc-598: Aluminum Desmut Concentrate	Novamax Technologies	
5377612	Solderstrip Str-B	Atotech	Liquid
5282225	Solution of hydrogen peroxide	Chester Labs	Liquid
5097559	Spe-De-Way Wood Bleach Unit A	Wood-Kote Products	Thin liquid
5801604	Super Cess-Flo	Degussa	Colorless liquid
3985144	Super Neutride Peroxide 20 Volume	Helene Curtis	Clear liquid
4227405	Super Neutride Peroxide 30 Volume	Helene Curtis	Clear liquid
5690931	Urine stain remover	Worldwide Supply	Liquid
2652827	Welloxide Stabilized 20 Volume Clear Peroxide	Wella	
2652835	Welloxide tablets	Wella	
2058752	Wood Bleach Solution B	Klean-Strip	
5266849	Wood Bleach Solution B 409.1	Klean-Strip; El Pico; Gillespie; Kwik; P & D; Duffy's	
4648387	Wood Bleach Solution Kit	W.M. Barr	