

Study conclusions

Clinical signs of brain injury are insensitive indicators of ICI in infants. A substantial fraction of infants with ICI can be detected through plain x-ray imaging of all infants with significant scalp hematomas, even if they are otherwise asymptomatic. Asymptomatic infants older than 3 months of age without significant scalp hematoma may be safely managed without any imaging.

Commentary

The finding of ICI in a significant proportion of infants who have no clinical signs of brain injury is startling, but before we mandate CT scans for everyone, 2 serious limitations of the study should be considered. First, only 31% of the study subjects underwent CT. Clearly some process was used to determine who would receive a CT, but the nature of that process is unknown. Whatever it was, it involved more than the information recorded by the authors, because only 59% of the “symptomatic” group were scanned, while 10% of those without even a hematoma were scanned. This introduces a selection bias that makes the study irreproducible. It also guarantees that any ED that institutes the authors’ recommended policy will obtain different results — unless they inadvertently follow the same undefined selection criteria for imaging. The study would have been stronger had all patients undergone imaging; however, this would have required the authors to obtain informed consent from patients — something that was not done.

Second, the primary outcome defined in the study (presence of ICI on a radiology report) is a surrogate endpoint for the real outcome of interest (clinically important ICI requiring treatment). It is a CT outcome, not a patient outcome. To illustrate this, of the 14 asymptomatic patients with ICI, 5

were discharged from the ED, and only 2 of the 9 who were admitted had an intervention (one child underwent surgical evacuation of an *asymptomatic* epidural hematoma and the other received prophylactic anticonvulsants).

The authors’ imaging recommendations imply that it is important to detect asymptomatic ICI, yet 69% of their study patients were discharged without CT and may well have had such an injury. The authors boldly state that, based on their follow-up data, no ICIs were subsequently diagnosed in the 420 patients who were discharged from the ED without head CT. However, this flies in the face of their own study conclusions, which are that “silent” ICI are not reliably detected by any combination of clinical symptoms.

An interesting observation from the study was the correlation between significant scalp hematoma and positive skull x-ray in infants less than 2 months of age. This suggests skull x-rays may be a useful screening tool for infants in smaller centres without CT availability, although a better correlation with patient outcomes would make x-rays more worthwhile. In centres with CT capability there is little reason to think that plain skull films will add value. This study does demonstrate that relatively asymptomatic ICI can occur and that it is more likely in infants under 2 months of age. The authors did not show, however, that patients will benefit from having their ICI detected; nor did they prove that their recommended strategy reliably detects asymptomatic ICI.

All of this is too bad, because the study had sufficient power to give us better guidance if these issues had been addressed in the study design phase. Now we will have to await another large study to answer the questions left behind by this one.

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Hyperbaric oxygen therapy in carbon monoxide poisoning: effects on neurological sequelae

Clinical question

Is hyperbaric oxygen superior to normobaric oxygen for preventing neurologic sequelae in carbon monoxide (CO) poisoned patients?

Article chosen

Scheinkestel CD, Bailey M, Myles PS, Jones K, Cooper DJ, Millar IL, et al. Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomized controlled clinical trial. *Med J Aust* 1999;170:203-10.

Reviewers

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Date appraised: Nov. 7, 1999

This article has been peer reviewed.

The search

National Library of Medicine, PubMed, MEDLINE

MeSH headings: carbon monoxide AND poisoning
(5 years, human, all studies)
Yield: 57 citations

The evidence

Design: A double-blind randomized controlled trial with 1-month follow-up.

Population: Over a 28-month period, 230 patients with CO poisoning were referred to a hyperbaric unit. Of these, 191 who received treatment within 24 hours of exposure were enrolled. Pregnant women, children and burn victims were excluded. Eligible patients were stratified based on the need for mechanical ventilation and severity of poisoning. Severe poisoning was defined as: mini-mental status score ≤ 24 , carboxyhemoglobin level over 30%, confusion, focal neurological deficits, loss of consciousness, ECG abnormalities, arrhythmias, pulmonary edema, metabolic acidosis, hypotension, convulsions, cardiac arrest or need for mechanical ventilation.

Intervention: All patients underwent 100-minute treatments in a hyperbaric chamber on 3 successive days. Hyperbaric oxygen (HBO) patients received 60 minutes of HBO therapy at 2.8 atmospheres plus 40 minutes of 100% oxygen. Normobaric oxygen (NBO) patients received 100 minutes of 100% oxygen at 1.0 atmosphere. NBO patients underwent “sham” treatment, whereby the chamber was flushed regularly to simulate pressurization. Treatment was extended to 6 days for patients who were clinically abnormal or who had poor neuropsychological parameters after 3 treatments. All patients received continuous high-flow oxygen between chamber exposures.

Outcomes measured: Patients underwent neuropsychological testing at baseline, after treatment (at 3 or 6 days), and at 1 month. Persistent neurologic sequelae (PNS) was defined as failure to improve to pre-treatment levels after oxygen therapy. Delayed neurologic sequelae (DNS) was defined as post-treatment improvement to normal, followed by a deterioration over days to weeks.

Results: 73% of the patients had severe CO poisoning, and mean time to treatment was 7.1 hours. Prognostic baseline variables (proportion treated within 4 hours of exposure, proportion requiring mechanical ventilation, CO level, and number of severe poisonings and accidental poisonings) were balanced between groups, suggesting adequate randomization.

After 3 days of treatment, 28% of HBO patients and 15% of NBO patients had abnormal neuropsychological tests ($p = 0.01$). For patients with severe poisoning, these figures were 35% and 13% respectively ($p = 0.001$). The incidence of persistent neurological sequelae (PNS) was 71% at discharge and 62% at 1-month follow-up, with no significant difference between groups. Five patients (2.6%) had

delayed neurologic sequelae (DNS) at a median of 40 days after treatment. All 5 belonged to the HBO group. At follow-up, NBO recipients scored significantly better on 1 of 7 neuropsychological tests (the Rye auditory verbal learning test) and the same on the others.

Conclusion

HBO therapy did not improve neuropsychological outcomes in this heterogeneous group of CO poisoned patients.

Comments

Carbon monoxide poisoning is common^{1,2} and hyperbaric facilities are not. HBO therapy is costly and relatively inaccessible in Canada and other countries with low population densities and long transport times. This well designed randomized clinical trial suggests that, while high-flow oxygen may be important, HBO does not improve neuropsychological outcomes after CO poisoning.

The incidence of PNS in this study (71% at discharge and 62% at follow-up) is high compared to previous studies.³ This probably reflects the high proportion of severe poisonings (73%) and suicide attempts (69%), as it is known that suicidal patients are often depressed and tend to score poorly on neuropsychological testing.

To put their results in context, the authors discuss 6 prior randomized studies of HBO therapy in CO poisoned patients. Two of these (combined $n = 91$) showed benefit while 4 (combined $n = 1395$) showed none. The current study is the first randomized trial to use standardized treatment and follow-up protocols as well as “sham treatment” for controls. Other studies have chosen not to include “sham” treatments because of the risk of chamber-related complications.^{3,5}

Advocates of hyperbaric oxygen therapy suggest that treatment is most effective when applied within 6 hours of exposure. In this study, mean time from exposure to treatment was 7.1 hours, and it is conceivable that the delay may have limited HBO's potential efficacy. To address this concern, the authors performed a retrospective subgroup analysis of patients who presented from 0–3 hours, 3–6 hours, 6–12 hours and >12 hours. This analysis failed to show a time-dependent HBO treatment effect.

It is interesting to note that — based on number of treatments, treatment duration, and the administration of high-flow oxygen between chamber exposures — patients in the Scheinkestel study received a higher total oxygen dose than those in previous studies. In this study, HBO patients received oxygen therapy equivalent to 35.7 carboxyhemoglobin dissociation half-lives and NBO patients received the equivalent of 28.5 dissociation half-lives. In previous studies, patients received between 7 and 18 carboxyhemoglobin dissociation half-lives.

globin dissociation half-lives. Since total oxygen dose may be an important determinant of outcome,^{3,8} it is possible that the NBO group in this study did relatively better because of the higher administered oxygen dosage.

An important drawback to the study is the fact that the investigators achieved only 46% follow-up at 1 month. While this rate is comparable to previous studies, it raises the possibility that patients lost to follow-up might have done significantly better or worse than those captured. If so, the true outcomes could differ from the reported outcomes.

Readers should also remember that these findings may not apply to pregnant women, children and burn victims, and that the methodological problems described above raise minor concerns about the study conclusions.

Clinical bottom line

This study is compatible with the bulk of previous literature. It suggests that most patients can be managed with NBO and that HBO does not improve neuropsychological outcomes after CO poisoning — especially in severely poisoned patients like the ones studied. Emergency physicians who manage CO poisoned patients without a hyperbaric facility will take comfort from these findings; however, it is still possible that some subgroups do benefit from HBO, and it may be prudent for physicians to collaborate with local hyperbaric facilities to establish protocols for dealing with specific patient groups.

COMMENTARY

The non-utility of HBO for CO poisoning?

Michael Boulanger, MD

The optimal time window for HBO after CO poisoning has yet to be determined, but the current standard is within 6 hours of exposure, and benefit seems most likely if treatment is started much earlier, although this is not known. In the Scheinkestel study, most patients had severe poisoning and the median time to treatment was over 7 hours. Based on severity and time to treatment, much CNS damage could have occurred prior to the administration of HBO. In other words, many of these patients may have been (rela-

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tively) beyond help, therefore unable to benefit from the treatment administered. In addition, most of the patients in this study were depressed and suicidal. Such patients score poorly on the neuropsychological tests used to evaluate outcomes, and this may have influenced the study results.

Current recommendations of the Undersea and Hyperbaric Medical Society (UHMS) and European Committee for Hyperbaric Medicine are that hyperbaric oxygen is indicated for patients who experience neurological or cardiac symptoms after CO exposure. These recommendations will likely not change based on this single study.

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