Comparison of normobaric vs. hyperbaric oxygen in the relief of carbon monoxide headache pain

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ABSTRACT

Background: Headache is the most common symptom in carbon monoxide (CO) poisoning. While the mechanism of CO-induced headache is not well defined, it is felt that cerebral vasodilation plays a role. Clinical experience has demonstrated oxygen breathing is effective in resolving CO headache. However, the effectiveness of normobaric oxygen has never been compared to hyperbaric oxygen in this regard.

Methods: A 2016 paper by Ocak, et al. reported the response of CO headache pain severity to four hours of normobaric oxygen breathing in 82 patients using a 0-10 analog scale. The demographics, carboxyhemoglobin levels and response to therapy from that report were compared to data obtained by Hampson, et al. in an earlier study, but never published, using the same pain assessment method in 73 patients with CO headache and treated with hyperbaric oxygen.

Results: Comparing the normobaric and hyperbaric groups, neither average age nor presenting carboxyhemoglobin levels were significantly different. Baseline pain intensity scores were 6.5 ± 3.1 vs. 6.2 ± 2.6 (p=0.444) and post-treatment scores 1.5 ± 2.6 vs. 1.0 ± 1.5 (p=0.184) respectively on a 0-10 scale.

Conclusions: In these two well-matched populations of patients with CO-induced headache pain, degree of resolution was not significantly different between normobaric and hyperbaric oxygen treatment.

INTRODUCTION

Headache (HA) is the most common symptom of acute carbon monoxide (CO) poisoning, occurring in more than one-half of patients in every large published series [1,2]. The mechanisms by which CO causes headache are incompletely understood [3,4]. Clinical experience, however, has demonstrated that oxygen breathing is associated with improvement or resolution of CO-induced headache.

The characteristics of the headache resulting from CO poisoning have been previously described by Hampson and Hampson in 100 consecutive CO-poisoned patients referred for hyperbaric 100% oxygen (HBO_2) treatment and who experienced headache with their episode [5]. Among those with headache at the time HBO_2 therapy was initiated, 97% improved with HBO_2, and 44% experienced total resolution. Severity of headache prior to and after HBO_2 was graded, but not included when the other descriptive information about CO-induced headache was published.

A 2016 study by Ocak and co-workers from Turkey randomized patients with CO-related headache to normobaric 100% oxygen (NBO_2) for four hours or NBO_2 plus one of two medications [6]. They found that headache resolution was equivalent in all three groups and suggested that the medications used in their study did not enhance recovery over NBO_2 alone.

There are no published studies comparing the effectiveness of NBO_2 versus HBO_2 for resolution of CO-induced headache. As the severity of headache pain was measured by the same method in both studies, this analysis was performed to compare NBO_2 and HBO_2 with regard to resolution of CO-induced headache pain.

KEYWORDS: carbon monoxide; headache; hyperbaric oxygen; normobaric oxygen; carboxyhemoglobin

	normobaric oxygen n=117	hyperbaric oxygen n=73	P-value
age (years)	38 ± 10	39 ± 13	P=0.583
gender	68F/49M	27F/46M	P=0.0001
carboxyhemoglobin (%)	21.4 ± 12.0	21.6 ± 9.8	P=0.898
common CO sources	stove 65%	motor vehicle 38%	
	water heater 15%	forklift 26%	
	natural gas burning 14%	furnace10%	

TABLE 1. Demographic and presenting carboxyhemogobin levels for patients with CO-induced headache treated with normobaric and hyperbaric oxygen

METHODS

In Ocak's 2016 study [6], 117 patients were prospectively randomized to one of three treatment arms for CO-induced headache. These included NBO_2 breathing for four hours, identical NBO_2 plus metaclopramide, or NBO_2 plus metamizole (a drug with analgesic, antipyretic and spasmolytic properties not available for human use in the United States). Demographic data were collected, along with baseline and serial subjective patient assessments of pain on a 0-10 analog scale. The Ethics Committee of Abant Izzet Baysal University Medical Facility approved the study.

When analyzed, there were no significant differences among the three groups with regard to age, gender or baseline carboxyhemoglobin (COHb) levels [6]. Similarly, baseline and post-treatment pain scores were not significantly different among groups. As it appeared that the medications chosen for study had no discernible effect, patients in the three groups were combined into one NBO_2 treatment group for this analysis.

In the earlier study by Hampson, age, gender, CO source, and baseline COHb levels were also collected. In addition, subjective patient assessment of HA pain on a 0-10 analog scale was performed prior to HBO_2 treatment and upon its conclusion. The HBO_2 treatment involved compression to 3.0 atmospheres absolute (ATA) with administration of two 23-minute 100% oxygen breathing periods separated by a five-minute air break at that pressure, subsequent decompression to 2.0 ATA over five minutes with administration of two 25-minute oxygen periods at that pressure, and then a 10-minute decompression to 1.0 ATA. Total treatment time was 121 minutes plus variable compression time, dependent upon patient tolerance.

Patient unidentifiable demographic and clinical information was recorded on a CO poisoning clinical research database approved by the Institutional Review Board of Virginia Mason Medical Center.

Of 117 patients treated with NBO_2 in the Ocak study, 82 completed the protocol, with the others dropping out because they either could not adapt to the treatment or voluntarily left the emergency department before the four-hour evaluation time point [6]. Remaining in the study for post-NBO_2 evaluation were 47 in the NBO_2-only group, 36 in the NBO_2-plus-metaclopromide group, and 34 in the NBO_2-plus-metamizole group. Baseline data for the total NBO_2 group therefore includes 117 patients with intent-to-treat while post-treatment data are from 82 who completed treatment.

Of the 100 CO-poisoned patients who were referred for HBO_2 with headache [5], 73 still had pain at the time of presentation to the hyperbaric department. Those 73 comprised the HBO_2 study population. All completed the planned HBO_2 treatment.

Statistical analysis was performed using the online program QuikCalcs from GraphPad Software [7]. Descriptive statistics (mean, SD) of continuous variables (age, COHb, pain scores) were calculated for the HBO_2 group and compared with NBO_2 data by unpaired t-test entering mean, standard deviation and number of patients. Categorical data were compared with two-tailed Fishers exact test.

RESULTS

Demographic and clinical information for the NBO_2 and HBO_2 groups are shown in Table 1. There were no significant differences between the two populations with regard to age or presenting COHb level.

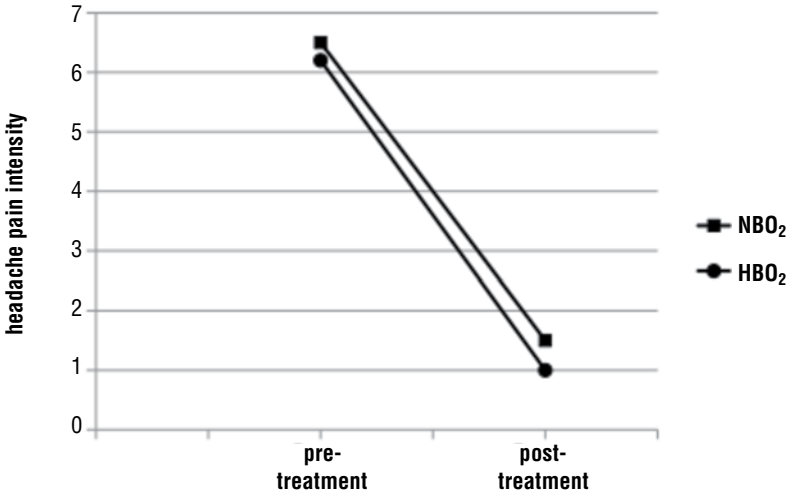

FIGURE 1: Response of CO-induced headache pain to normobaric oxygen (NBO_2) and hyperbaric oxygen (HBO_2). Pain intensity scores are the mean for each group, based on a 0-10 scale.

The NBO_2 group was 58% female, while the HBO_2 group was 37% female (P=0.001). This appears to relate to the source of poisoning and associated domestic or work activities. Table 1 lists the three most common CO sources in each population. Females predominated in the Turkish population, and the common sources were related to the home. Males predominated in the U.S. population, with motor vehicles and forklifts resulting in approximately two-thirds of the poisonings.

Baseline headache intensity averaged 6.5 ± 3.1 in the NBO_2 group and 6.2 ± 2.6 in the HBO_2 group ($P = 0.444$). Pain score following four hours of NBO_2 was 1.5 ± 2.6 and 1.0 ± 1.5 following one HBO_2 treatment ($P = 0.184$) (Figure 1).

DISCUSSION

CO has a number of mechanisms of toxicity. These include binding to hemoglobin, with associated reductions in arterial blood oxygen content and oxygen delivery; intracellular protein binding, causing interruption of high-energy phosphate production (myoglobin, cytochrome a,a3); nitric oxide production, with peroxynitrite production and neutrophil activation; lipid peroxidation by neutrophils; mitochondrial oxidative stress; apoptosis; immune-mediated injury; and delayed inflammation [4]. When they have been compared, laboratory models of CO toxicity have consistently shown that the mechanisms identified are modulated more favorably by HBO_2 than NBO_2 [8-12].

Clinical studies comparing NBO_2 with HBO_2 in CO poisoning have typically used neurologic injury as the measured outcome, usually by assessing long-term cognitive function. None have compared resolution of clinical symptoms, including whether one method of oxygen administration is more effective than the other for the most common symptom in CO poisoning, headache.

Oxygen administration is standard initial treatment in CO poisoning [4], first reported to have been utilized by Linas in France in 1868 [13]. It has long been known that oxygen breathing accelerates the clearance of COHb. While NBO_2 has been extensively compared with normobaric air breathing in regard to COHb half-life in humans [3], there is no trial demonstrating that NBO_2 has a clinical treatment advantage over air. It would likely be considered unethical to perform such a study today, as oxygen therapy is the accepted standard of care worldwide, it is inexpensive, and relatively non-toxic. While NBO_2 and HBO_2 were demonstrated to relieve CO-induced headache intensity to an equal degree in this comparison, it is assumed that both are more effective than air.

As noted previously, the mechanism for CO-induced headache is poorly defined. CO headache was traditionally described as throbbing, likely related to a table published in a 1923 Bureau of Mines report that was widely copied in the literature for decades [14,15]. This table listed symptoms to be expected at various COHb levels and indicated that "Headache; throbbing in the temples" occurred at a level of 20%-30%. It is now generally believed that neither symptoms in general nor severity of CO-induced HA in particular correlate with presenting COHb levels [1,5,6]. Further, there is no "characteristic" HA caused by CO, and it is certainly not bitemporal and throbbing. In the prospective evaluation of headache characteristics in CO-poisoned patients, only a minority experienced throbbing pain. and the most frequent location was frontal [5].

If the assumption that 100% oxygen breathing accelerates headache resolution better than air is correct, the mechanism by which it does so is speculative. It is unlikely to be an effect on any of the toxic mechanisms of CO listed above because HBO_2 has been demonstrated in animal models to modulate most of them more favorably than NBO_2. It cannot simply be reduction in COHb level because HBO_2 does this more efficiently than NBO_2 and COHb has been shown not to correlate to peak CO headache pain intensity [5,6].

The vasoconstrictive effects of oxygen may be the mechanism for pain relief in CO-induced headache. Acute hypoxia is a potent dilator in the cerebral circulation that produces marked increases in cerebral blood flow [16]. Additionally, CO itself is an endogenous vasodilator, mediating vascular smooth muscle cell relaxation via cyclic GMP [17]. In a rabbit model, 1% CO administration reduced cerebrovascular resistance by 70%-76% and increased cerebrocortical blood flow by 230%-290% despite a 28% fall in mean arterial pressure [18].

There are at least two mechanisms by which oxygen may be causing vasoconstriction. First, it may inhibit hypoxia-induced vasodilation by improving tissue oxygenation. Secondly, oxygen has primary vasoconstrictor effects in the systemic circulation. Kenmure and colleagues demonstrated in 1948 in humans that hyperbaric 100% oxygen breathing at 2.0 ATA increased systemic vascular resistance (SVR) 15% above that seen with normobaric air breathing [19]. NBO_2 caused an increase in SVR similar to that seen with HBO_2. Berry and co-workers studied regional blood flow effects of hyperoxia in a canine model [20]. NBO_2 administration increased SVR 24% over that measured breathing air. Carotid flood flow was unchanged from air with NBO_2 and reduced 18% with HBO_2 at 2.0 ATA.

These changes are supported by a variety of studies looking at cerebral blood flow (CBF) during hyperoxia. Compared to air breathing, Kety reported a 13% decrease in CBF caused by NBO_2 [21], while Lambertsen measured a 15% decrease in CBF with NBO_2 and a 25% reduction breathing HBO_2 at 3.5 ATA [22], both studies in humans. Bergo and Tyssebotn reported a 30% reduction in CBF in rats breathing HBO_2 at 3.0 ATA and a 23-32% decrease when breathing 95% oxygen at 5.0 ATA [23,24].

Vasodilation is a recognized cause of many types of headache, examples of which are hypobaric hypoxic headache at altitude and hypercapnic headache [25]. Oxygen has been demonstrated in a prospective, randomized fashion to be effective treatment in cluster headache [26] and in primary headache disorders of mixed type in patients presenting to the emergency department [27]. The clinical response to oxygen administration seen in the present comparison is comparable in time course and direction to the human experimental studies on vasoconstriction described. It is interesting to note that the laboratory investigations reported suggest that a large portion of the oxygen-induced reduction in CBF occurs with NBO_2 administration. This is consistent with the present clinical finding that NBO_2 and HBO_2 at 3.0 ATA relieved CO headache pain similarly.

LIMITATIONS

It was fortuitous that the study by Ocak used the same methodology for headache pain scoring as was used in the earlier CO headache investigation by Hampson, allowing direct comparison of results. The numbers of patients were similar, with matching mean patient age and COHb levels. A potential limitation could be the mismatch of gender and CO sources. However, no differences in response to CO poisoning treatment by gender or source have ever been reported, so it would be difficult to argue that they are having an effect here.

Another potential limitation could be cultural differences between the normobaric and hyperbaric populations influencing subjective assessment and reporting of pain. It is noted that pre-hospital treatment information

is not available for comparison and that post-treatment assessments were performed at different times because the treatments were of different durations. As pain intensity was formally assessed only pre- and post-treatment, it is not possible to say whether one of the two forms of oxygen administration relieved pain more rapidly.

CONCLUSION

In summary, oxygen administration is associated with marked reduction in the intensity of CO-induced headache pain, and the degree of reduction appears similar whether four hours of NBO_2 or a two-hour HBO_2 protocol for CO poisoning is utilized. Oxygen likely has its effect by inhibition of cerebral hypoxia-induced vasodilation and direct cerebrovascular constriction. ■

Conflict of interest statement

The authors declare that no conflicts of interest exist with this submission.

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