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Brief Research Report

Demand Valve Oxygen: A Promising New Oxygen Delivery System for the Acute Treatment of Cluster Headache

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Abstract

Objective. To show that demand valve oxygen is an effective acute treatment for cluster headache and to compare this oxygen delivery technique with standard cluster headache therapy of continuous flow oxygen.

Methods. Single-center, open-label, two-period, two-treatment crossover design, pilot study was used. Subjects treated with one of two sequences: first, headache treated with continuous flow oxygen (100% oxygen at 15 liters per minute), and subsequent with demand valve oxygen, or vice versa. Treatment began when pain was at least moderate. Subjects taught a specific breathing technique for demand valve oxygen that included initial period of hyperventilation. Primary end point was headache response (moderate-to-very-severe pain reduced to mild or none) after 30 minutes of treatment.

Results. Three subjects completed the trial, while a fourth completed demand valve oxygen only. All had chronic cluster headache. All subjects treated with demand valve oxygen became pain-free (time in minutes: 15, 19, 6, 8). Three of four had no recurrence within 24 hours. Demand valve oxygen reduced cranial autonomic symptoms in all and resolved them in two subjects. For continuous flow oxygen, two of three subjects became pain-free (20, 10 minutes). Continuous flow oxygen reduced but did not eliminate cranial autonomic symptoms. Continuous flow oxygen had higher recurrence rates. No adverse events noted with either treatment.

Conclusion. Demand valve oxygen appears to be an effective acute treatment for cluster headache. All subjects became headache-free. Time to pain freedom was fast (average 12 minutes). The small number of study subjects does not allow a direct comparison of efficacy between demand valve oxygen and continuous high flow oxygen.

Key Words. Cluster Headache; Oxygen; Oxygen Delivery Systems; Trigeminal Autonomic Cephalalgias; Continuous Flow Oxygen; Demand Valve Oxygen

Inhaled continuous flow oxygen (CFO) has been a mainstay of cluster headache (CH) treatment since the landmark study by Kudrow in 1981 [1]. Patients were treated with 100% oxygen at a rate of 7 liters per minute (LPM). There is recent recognition that higher flow rates of oxygen (12–15 LPM) are more efficacious than lower flow rates [2,3]. CFO, in the currently prescribed dosing strategy using a non-rebreather face mask, is not effective for all CH sufferers, and time to onset is not as fast as injectable sumatriptan [3]. Could a different oxygen delivery system that provides higher oxygen flow rates and an assured 100% oxygen concentration be more efficacious in CH treatment? A demand valve delivers oxygen to the user as soon as they try to inhale from an attached mask, thus dosage is controlled by respiration rate and tidal volume. If the user inhales more deeply, more oxygen will flow in response to the increased demand, hence the name. Unlike a CFO regulator, a demand valve is capable of delivering 100% oxygen from 0 to 160 LPM. One benefit of demand valve is that it can support hyperventilation. CFO regulators are typically limited to 15 LPM, thus incapable of supporting hyperventilation. Hyperventilation leads to a state of hyperoxia and hypocapnia. Both conditions cause cerebral arterial vasoconstriction, a possible mechanism by which CH pain is relieved [4]. Hyperoxia also inhibits neurogenic inflammation elicited by trigeminal ganglion stimulation, an event in CH pathogenesis [5]. In addition, based on its mechanics, demand valve assures delivery of 100% oxygen without dilution by room air. (Figure 1). This issue however plagues the CFO with non-rebreather face mask systems currently utilized for CH therapy, as room air typically leaks into the gas inhalation stream through the masks, resulting in reductions (sometimes significant) in oxygen concentrations delivered to the CH sufferer. Because demand valve oxygen (DVO) can support hyperventilation, very high flow rates, and delivers 100% oxygen without dilution, it should be effective in the acute treatment of CH and theoretically more effective than CFO given via a non-rebreather face mask.

Methods

This study was approved by the Geisinger Institutional Review Board.

Single-center, open-label, two-period, two-treatment cross-over design, pilot study was the method used to investigate the effectiveness of DVO with a specific breathing technique for the acute treatment of CH. The study would also test if DVO is more effective than high flow rate CFO. The goal was for 12 subjects to be recruited. Every other subject (including the initial study subject) treated the first headache with high flow rate CFO (100% oxygen at 15 LPM via non-rebreather face mask) and the subsequent headache with DVO, while the remainder would treat with DVO first and CFO second. The two treated attacks needed to be separated by at least 24 hours. Subjects could not take acute medication within 6 hours of oxygen treatment. The study subject was allowed 10 days to complete the two treatments. Inclusion criteria included individuals age 18–65 years that met International Classification of Headache Disorders, 2nd edition criteria for episodic or chronic CH, and who had attacks that lasted at least 45 minutes in duration [6]. Exclusion criteria included a history of COPD or uncontrolled asthma, and/or a history of syncope or extreme lightheadedness with hyperventilation. Past response or nonresponse to oxygen was not an exclusion, and patients could be on preventive medication with no recent changes in dose or medication type. Subjects were recruited from Geisinger Health System patients and from CH patient organizations.

All subjects received a questionnaire to be completed with each of the treated headaches. Prior to treatment, the subjects graded their pain on a five-point scale (1 no pain to 5 very severe pain) that has been utilized in previous acute CH treatment studies [7]. The questionnaire also assessed need for rescue medication, any adverse

Figure 1 Image of a demand valve with attached face mask. A demand valve is directly connected via a simple high-pressure gas line to a high-pressure output port on the oxygen cylinder regulator. A demand valve must be held firmly against the face to affect a total seal for the valve to activate upon inhalation and deliver 100% oxygen. If the mask to face contact seal is broken, the mask does not work. For demand valve, there are no additional pathways or components such as the holding bag and valve connections in non-rebreather mask systems typically used for cluster headache therapy where air can enter the system, nor in particular where air can enter the system where the mask touches the face that dilutes the concentration of oxygen delivered.

events, and headache recurrence at 30 minutes post-treatment and at 24 hours post-treatment. Patients were also asked how DVO is compared with prior acute treatments and if they would use DVO again if they had the opportunity. Oxygen inhalation commenced when the subject's head pain intensity level was at least moderate and would stop after 30 minutes of treatment. Subjects assessed their pain at 5, 10, 15, 20, 25, 30, 45, and 60 minutes using a stopwatch. Escape medication was allowed at 60 minutes.

DVO Administration Protocol

Subjects were instructed on a specific breathing technique with DVO. They practiced the technique with staff, and if they experienced any major adverse events (e.g., syncope), they were excluded from the study (this did not occur). Breathing protocol was initiated by taking three to four very deep slow breaths. The subject would then increase their respiration rate to one complete cycle every 2 seconds (hyperventilation) for 1 minute or until they developed paresthesias (whatever came sooner) at which time the rate was slowed to one respiration cycle every 3–4 seconds, and this would continue until pain freedom or 30 minutes of treatment. If pain freedom was achieved prior to 30 minutes, the subject would resume a normal respiration rate. The DVO protocol was established by two CH sufferers who had extensive knowledge of pulmonary physiology and had utilized DVO for their own attacks.

Primary end point was headache response (reduction in CH intensity from moderate-to-very-severe pain to mild or no pain) after 30 minutes of treatment. Secondary end points included: percentage with no pain, reduction of cranial autonomic symptoms, CH recurrence within 24 hours, and likelihood of choosing this technique again.

Statistical Analysis

No statistical analysis could be completed secondary to a very small study sample size (see later).

Results

Three subjects completed the trial (two male, one female), while a fourth (male) completed the DVO arm only (no subsequent attacks during the study period). All subjects had chronic CH, and all were past or present smokers. The study was halted after 1 year because of poor recruitment. In reality, there were multiple inquiries about the clinical trial from many patients who lived outside of the study geographic area, including individuals from Europe, but we could not identify enough local patients to reach our targeted goal. Full results and demographics from the study are in Table 1. All subjects who treated with DVO became pain-free (time in minutes: 15,19, 6, 8). Average time to pain freedom was 12 minutes. Average time to therapeutic response (going to mild or no pain) was 10 minutes. There was no recurrence of headache at 30 minutes post-treatment in all study subjects, and three of four had no recurrence within 24 hours of treatment. No

Table 1 Demand valve oxygen

Study Subject	Gender (Age in Years)	Cluster Headache (CH) Type	Smoking History	Duration of Untreated Attacks/# of Attacks per Day	Pain Level at Onset of Oxygen Treatment	Pain Level after Oxygen Treatment	Time to Response in Minutes (Mild or No Pain)	Time to Full Effect in Minutes	Recurrent Headache within 24 Hours Post-treatment	Resolution of Cranial Autonomic Symptoms with Treatment
Subject 1	M (62)	Chronic CH	Current	60 minutes/2 attacks						
Continuous flow					Moderate	No pain	15	20	No	No, but reduced
Demand valve					Moderate	No Pain	10	15	No	No, but reduced
Subject 2	F (46)	Chronic CH	Current	120 minutes/2 attacks						
Continuous flow					Severe	Mild	30	30	Yes	No, but reduced
Demand valve					Severe	No pain	15	19	No	No, but reduced
Subject 3	M (50)	Chronic CH	Past	60 minutes/1 attack						
Continuous flow					Moderate	No pain	10	10	Yes	No, but reduced
Demand valve					Severe	No pain	6	6	Yes	Yes
Subject 4	M (53)	Chronic CH	Current	60 minutes/2 attacks						
Continuous flow					—	—	—	—	—	—
Demand valve					Moderate	No pain	8	8	No	Yes

subject needed rescue medication. In regard to cranial autonomic symptoms, DVO reduced the number of symptoms (e.g., going from two symptom-conjunctival injection and eyelid droop to one symptom) in all four subjects, and the symptoms completely resolved in two subjects. All subjects rated DVO better or much better than their prior CH abortive treatments of which two had used oxygen. All subjects stated that they were likely or very likely to use DVO again. For CFO, two of three subjects became pain-free (time in minutes: 20, 10), while a third had positive headache response but only to mild pain, and this took 30 minutes. Average time to pain response was slower than for DVO at 18 minutes. Two of the three subjects on CFO had a recurrence of CH within 24 hours of treatment. All subjects on high flow rate CFO had a reduction in the number of cranial autonomic symptoms, but none had resolution. There were no adverse events with either form of oxygen delivery.

Discussion

Inhaled CFO via a non-rebreather face mask is a mainstay of acute CH treatment. It is safe and seemingly effective in studies [1,2]. However, in the real world, CH sufferers are not using oxygen. In a survey study from the United States, 70% of the CH population (1134 individuals) felt that oxygen was effective, but only 25% were using oxygen [3]. Several reasons were suggested including oxygen's ease of use, and time to onset does not favorably compare with injectable sumatriptan that does not require special equipment and is faster to effect. A main reason to complete the current investigation was to address the oxygen treatment gap issue to see if an alternative delivery system could be more effective and provide faster relief compared with CFO. Based on a very small study sample size, DVO with a specific breathing technique appears to be an effective acute treatment for CH. All patients studied had chronic CH that is known to be less responsive to oxygen therapy than episodic CH, and all subjects became headache-free with DVO [1,3]. Time to pain freedom was fast with an average time of 12 minutes, while two of four subjects had pain freedom by 8 minutes or less. DVO appears to provide headache relief as fast as subcutaneous sumatriptan that in studies takes 10–15 minutes for response [8]. High flow CFO was also effective in all study subjects. Our data suggest that DVO might be superior to CFO on several fronts for acute CH therapy (faster time to headache response, higher rates of pain freedom, less headache recurrence, and better at alleviating cranial autonomic symptoms), but our small study sample size does not allow us to make any definitive statements comparing the efficacy of these two oxygen delivery systems. Oxygen in animal models of CH appears to act on the cranial autonomic nervous system rather than the trigeminal afferent system; thus, the hyperoxia associated with DVO treatment with hyperventilation and the delivery of nondiluted 100% oxygen at high flow rates may more thoroughly suppress the cranial autonomic nervous system and thus provide more complete resolution of autonomic symptoms and a higher likelihood of pain freedom than CFO via a non-rebreather face mask that cannot generate the same levels of oxygen concentration in the cortex [9]. Finally, in regard to the safety of breathing nondiluted 100% oxygen at high flow rates, military pilots have for decades safely breathed these concentrations for many hours, while in flight at high altitudes and during combat have safely hyperventilated 100% oxygen for much longer periods than involved in this CH treatment method.

For the "real-world" CH patient out in the community, the technology for the DVO system (regulator with a demand valve port and demand valve with reuseable mask) is readily available from numerous online vendors. The medical oxygen cylinders (the same ones utilized for CFO systems) are available from any medical gas supply store or homecare provider. When looking at the economics of a DVO system vs a CFO system, the difference would be the one time cost of a regulator with a demand valve port and the demand valve with reuseable mask that currently costs about $500. Both systems utilize the same medical oxygen cylinders; thus, those costs would be equal. There is no difference in portability between DVO and CFO systems because both require the same type of oxygen cylinders. It is the oxygen cylinder that hampers portability for patients. CH sufferers will normally carry a small oxygen cylinder in their car for travel and for at work and then have a larger capacity cylinder for home use. The weight and size difference between a demand valve mask and CFO mask is negligible, thus would not affect portability.

In conclusion, the numbers of subjects studied is too small to make any definitive statements about DVO in CH treatment, but the results are promising. As the trial subjects were instructed to only treat one headache with each oxygen protocol technique, consistency of response for DVO could not be measured. This trial also utilized a specific breathing technique that promoted hyperventilation; thus, future investigations will need to assess if DVO with normal respiration rates or enhanced flow rates without hyperventilation are also useful, or the key to response is initial hyperventilation followed by high oxygen flow rates. The hope is that this small investigation will lead to future multicenter trials of DVO to prove efficacy and to add a new dimension to CH treatment.

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