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Research Article

Comparative Effectiveness of Hyperbaric Oxygen Therapy Versus Bevacizumab Therapy in Patients with Vascular Obstructions of the Retina

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Abstract

Aim: To compare the evidence of primary studies on the effectiveness of hyperbaric oxygen therapy and Bevacizumab in patients with retinal vascular obstructions.

Materials and methods: A systematic review was carried out without meta-analysis of 123 primary studies, 98 of which were excluded due to exclusion criteria, the remaining 25 studies were submitted to internal and external validity criteria, leaving 20 for research use.

Results: No significant differences were observed between the efficacy of hyperbaric oxygen therapy and Bevacizumab (0.73 and 0.78), respectively. In contrast, the cost of both benefits had a significant variation between both therapies ($20.70 and $475.42 dollars approximately).

Conclusions: Although both therapies have demonstrated efficacy in retinal vascular obstructions, the cost per individual benefit makes hyperbaric oxygen therapy more convenient and at the same time less invasive than other ophthalmologic treatments indicated for these pathologies.

Keywords: Hyperbaric Oxygen Therapy; Bevacizumab; Retinal Vascular Obstruction; Hyperbaric Chamber; RVCO; CRAO

Introduction

Retinal vascular occlusions are recognized as such since 1855 [1], and correspond to the second most frequent vascular pathology causing a variable decrease in visual acuity (VA), such decrease is directly related to the obstructed vessel, i.e., a large caliber vessel such as the central retinal artery or vein can be occluded, or it can affect smaller caliber vessels, such as the branches of the retinal artery or vein.

As the retina is one of the tissues of the human body with the highest metabolic rate expenditure [2], an affectation to its blood flow (total or partial) causes permanent damage to the vision of patients, therefore, the combination of a correct and immediate diagnosis plus an effective emergency treatment is crucial to ensure a higher success rate in the final visual function and avoid the appearance of irreversible complications. Unfortunately, at present, although there are multiple therapeutic approaches for these pathologies, conventional treatments do not present satisfactory effects; on the contrary, many have side effects or risks inherent to their application.

Hyperbaric oxygen therapy (HBO) is a non-invasive treatment modality [3], consisting of inhalation of 100% oxygen in a pressurized environment [4]. To date, there are few studies linking retinal vascular obstructions with conventional treatment modalities

(such as Bevacizumab) [5]. Therefore, it is imperative that new therapeutic options be evaluated so that these patients have greater access to effective treatments with fewer complications.

Materials and Methods

A systematic review without meta-analysis of 123 primary studies that have evaluated both hyperbaric oxygen therapy and Bevacizumab therapy in the treatment of retinal vascular obstructions was performed, such information was obtained thanks to the technique of documentary and bibliographic collection of primary studies.

Data collection

A wide and systematic literature review was carried out through the appropriate formulation of keywords in electronic databases. The key words or search terms were established under the PICOT model, synonyms and orthographic variations of these topics are also included to broaden the search options to find more articles, then thanks to the Health Sciences Descriptors or Thesaurus, the most suitable words to search for a topic are defined. From there, the search strategy is assembled through boolean operators to generate a much more sensitive search of the information.

Inclusion and exclusion criteria

The search for studies in the scientific literature was performed by means of a search strategy that included reading the title or abstract and/or reviewing the complete article. The unit of study was selected as those patients with a diagnosis of acute ischemic lesion of the retinal vessels, either central retinal artery or vein obstruction or its branches, with a symptomatologic onset of less than 24 hours for HBO or less than 12 months for BV. In accordance with the above, only the type of design corresponding to a "retrospective study" was included, in addition patients should not have contraindications for the treatments in question and VA is compared between the HBO group or the BV group to indicate improvement or not of the patient's final visual status.

Among the articles that were excluded from this study were those in which the patients did not present arterial or venous obstruction of the retinal vessels, if there was intervention in animal models, if the intervention to be evaluated was not with HBO, BV or combined treatments. Other exclusion criteria were that the symptomatologic onset was greater than 24 hours for HBO or greater than 12 months for BV, VA was not an endpoint and the type of design was not a "retrospective study".

The investigators, independently and according to the inclusion and exclusion criteria, made a selection process of the articles they consulted in search sources; disagreements were resolved by means of a consensus decision between them. Thus, 98 studies were excluded due to exclusion criteria.

Internal and external validity criteria

The remaining 25 studies were submitted to internal and external validity criteria in order to apply quality filters, using the CARE guidelines [6], such tables were adjusted to a weighting based on a relative weight and a respective score in order to have the studies with the best quality available, after this evaluation performed independently by both authors, leaving 20 studies for research use.

Construction of indicators

Units of analysis are extracted from the selected articles based on the systematization of variables and the information is analyzed using health indicators to obtain the results. The variables are presented and ordered in a contingency table for the construction of probabilistic indicators, as shown in table 1.

BV in vascular obstructions of the retina	**Gold standard therapy**		**Total**
	Positive	**Negative**	
Positive test	a	b	a+b
Negative test	c	d	c+d
Marginal totals	a+c	b+d	a+b+c+d
HBO in retinal vascular obstructions	**New Therapy**		**Total**
	Positive	**Negative**	
Positive test	a`	b`	a`+b`
Negative test	c`	d`	c`+d`
Marginal totals	a`+c`	b`+d`	a`+b`+c`+d`

Table 1: Contingency table for BV and for OHB.

These tables will be applied for both BV and OHB, to calculate:

- a and a`: Patients whose VA improved after the first intervention.
- b and b`: Patients whose VA improvement was with more than one intervention.

- c and c`: Patients who do not improve their VA after one intervention.
- d and d`: Patients who do not improve their VA regardless of the number of interventions.

Results

The results obtained after the selection process and subsequent analysis of evidence are shown in table 2, where the data obtained are represented numerically in contingency tables.

BV in vascular obstructions of the retina	**Gold standard therapy**		**Total**
	Positive	**Negative**	
Positive test	33	635	668
Negative test	13	176	189
Marginal totals	46	811	857
HBO in retinal vascular obstructions	**New Therapy**		**Total**
	Positive	**Negative**	
Positive test	0	193	193
Negative test	0	70	70
Marginal totals	0	263	263

Table 2: Performance indicators.

After observing the number of total patients treated with Bevacizumab, cells "b" and "b+d" of the respective contingency table were standardized to percentage (Table 3), in order to make both contingency tables comparable from a statistical point of view while eliminating the bias due to data asymmetry.

BV in vascular obstructions of the retina	**Gold standard therapy**		**Total**
	Positive	**Negative**	
Positive test	33	95	128
Negative test	13	26	39
Marginal totals	46	121	167

Table 3: BV table standardized to percentage.

The data from both contingency tables are represented in figure 1, where the difference between the two therapies to be compared is shown, together with the respective number of patients, so that the corresponding bar graph was made for better visualization of the results obtained.

Figure 1: Comparative efficacy between HBO and BV.

Efficacy was measured based on the split between patients whose VA improvement occurred with more than one intervention (b and b` for BV and HBO respectively) over patients who improve or not with more than one intervention (b + d and b`+d`). This result gave an efficacy for BV of 0.78 and 0.73 for HBO.

After consultation with multiple professionals who collaborated with the research and who work in these areas, the results shown in table 4 were arrived at. The values obtained involve costs for both therapies (human resources, supplies, etc.) to be compared, ranging from an annual cost (in dollars) for the center that works with HBO or BV, to a cost per individual service, i.e., what it would cost the system per patient treated.

	HBO	**BV**
Annual benefit cost	$ 200.422,92	$ 247.478,74
Monthly benefit cost	$ 16.701,91	$ 20.623,23
Daily service cost	$ 835,10	$ 1.031,16
Number of patients seen daily	40	2,15
Individual benefit cost	$ 20,88	$ 479,89

Table 4: Table of costs associated with both therapies.

Then, by dividing the efficacy of both therapies over their respective costs, it is possible to arrive at an indicator of effectiveness, that is, which treatment is more convenient. The results obtained are shown below in table 5.

	Efficacy of therapy	Technical requirement	Effectiveness
BV	0,78	479,89	0,001632
HBO	0,73	20,88	0,035146

Table 5: Table of results: efficiency, technical requirement and effectiveness.

Dividing the effectiveness of HBO over the effectiveness of BV results in HBO being 21.5 times more effective than BV.

Another result of the research was the creation of the care process map for patients with retinal vascular obstructions, that coordinates all the actions necessary for the processes or activities to occur during the clinical care of these patients in the event that they can be treated with HBO, as explicitly shown in figure 2.

The selection criteria are of utmost importance in this process, it is here where the Medical Technologist mention Ophthalmology (TMO) would suspect and refer to emergency HBO patients with acute vision loss in the appropriate case, as an emergency measure in patients who meet the following criteria that are internationally validated and protocolized by the Undersea and Hyperbaric Medical Society (UHMS) and would be evaluated nationally by the TMO: Presentation within 24 hours of vision loss; Corrected VA of 20/200 or worse; VA equal to 20/200 or worse with pinhole (CAE); Age >40 years; No pain associated with vision loss; No history of acute onset of flashes or floaters prior to vision loss; No history of recent eye trauma.

Initially, all patients with sudden loss or decrease of VA will go to their nearest Family Health Center (CESFAM), where they will be evaluated and referred by a General Practitioner to the Ophthalmology Primary Care Unit (UAPO), here the care will be handled by the TMO who acts as "gatekeeping", that is, as a filter, having the power to refer as he/she deems appropriate based on the results of his/her evaluation (framed in his/her performance in primary health care (PHC)). In the event that the patient presents with a decrease in VA not associated with a retinal vascular occlusive process, he/she will be referred to a general ophthalmologist at the secondary level of care; otherwise, if it is determined that the decrease in VA is the result of an acute occlusive process, he/she will be immediately referred to an ophthalmologist associated with the hyperbaric medicine center of reference, who will be in charge of determining whether or not the patient requires treatment with HBO. In summary, it would be the TMO who would initiate the care process, with its expanded role of "gatekeeping", based on established criteria, along with the results of tests performed at the time (medical history, VA, ophthalmoscopy and retinography).

Figure 2: Health care process map.

Discussion

Throughout our study, the comparative effectiveness of both hyperbaric oxygen therapy and Bevacizumab was demonstrated. The final results were obtained based on multiple correlated factors, firstly, the effectiveness of each therapy was measured according to a systematic review of multiple primary sources, extracting the corresponding units of analysis and standardizing them as a percentage according to contingency tables, on the other hand, the individual technical requirement according to cost-performance (human resources, supplies, physical space to apply the therapy), was obtained based on data provided by multiple professionals related to hyperbaric medicine and ophthalmology centers. Finally, by means of mathematical formulas, it was obtained that hyperbaric oxygen therapy is 21.5 times more effective than Bevacizumab.

A relevant aspect that caught our attention is the low number of publications relating hyperbaric chamber therapy and its application in ophthalmology. According to the results obtained, there is evidence of good efficacy (0.73) associated with a low cost per individual service (US$ 20.88), which makes it highly feasible to treat patients with retinal vascular obstructions on the basis of efficacy and individual cost.

Currently, hyperbaric medicine centers have proven to be feasible to implement, based on good administrative and human resource management. There have been multiple attempts to establish hyperbaric chamber therapy in Chile, however, the lack of scientific evidence makes it inadmissible for the national health system, this has led to the lack of protocols and technical standards that regulate their actions, therefore, patients are faced with a wide range of costs and benefits indicated by each medical center.

Conclusion

Retinal vascular obstructions continue without an approved treatment and conventional alternatives are not sufficiently effective, with little significant improvement in visual outcome. An example of this is Bevacizumab therapy, a procedure that requires multiple interventions or injections in the patient to achieve a certain efficacy maintained over time, and being an invasive technique, it is not free of complications. Therefore, an effective and non-invasive alternative is early management with hyperbaric oxygen therapy, which offers an improvement in visual function in most patients with retinal vascular obstructions who are treated early (less than 24 hours after the onset of the occlusive event) and to a lesser degree in those treated late. Although it is an effective and reliable therapeutic to address this pathology, more prospective controlled and larger scale studies are needed to confirm this.

The factors of efficacy and technical requirements are sensitive for the health system in Chile. In this case it is feasible to propose strategies to include hyperbaric oxygen therapy within the health care network, following the protocols established by the UHMS, in conjunction with the health care process map included in the research. The Medical Technologist mention Ophthalmology is part of the health care network, so he can collaborate with the clinical processes, thus increasing the benefits that patients of the Chilean public health system would have, consequently, increasing the opportunities for medical research and creating research niches, which would open the option of implementing hyperbaric oxygen therapy to other pathologies that are indicated for its use and thus increase the efficiency of the health care network.

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Conflict of Interest

The authors indicate no financial support or financial conflict of interest.

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