Arh hig rada toksikol 1993;44:239-247

Observation
UDC 617.7-007.681:615.835.12

HYPERBARIC OXYGEN DOSE OF CHOICE IN THE TREATMENT OF GLAUCOMA

L. Bojić[1], H. Kovačević[2], Đ. Andrić[2], D. Romanović[2] and N. M. Petri[2]

Department of Ophthalmology, New Hospital, Split, Croatia[1] and Department of Underwater and Hyperbaric Medicine, Naval Medical Institute, Split, Croatia[2]

Received August 31, 1992

The subjects in the study were 111 patients with open angle glaucoma who were submitted to treatment by hyperbaric oxygenation. Two groups were formed at random, an experimental one of 91 patients and a control group of 20 patients. The experimental group consisted of four subgroups classified according to the course of treatment they received: 30 sessions (31 patients), 20 sessions (20 patients), 15 sessions (20 patients) and 10 sessions (20 patients). For the treatment a large walk-in recompression chamber was utilized, once a day, at a pressure of 2.0 bars, for 90 minutes. Visual acuity and mean intraocular pressure values taken before and after hyperbaric oxygen treatment did not show a statistically significant difference either between the treated and control subjects, or at control examinations after three and six months. During the follow-up period, changes in the visual field area in control subjects were discrete and statistically not significant. At the same time the visual field values increased after the therapy in all the subgroups. In the 10-session course subgroup the increase was not statistically significant. In all other subgroups, statistical significance was at the level of $P<0.01$. Control after three months demonstrated the same level of statistical significance; control at the end of six months failed to show a statistically significant difference. The 20-session course is recommended for initial treatment. When visual field values return to 50 per cent of the improved values achieved during initial treatment, it is suggested that hyperbaric oxygen treatment be repeated.

Key terms: hyperbaric oxygenation, intraocular pressure, open angle glaucoma, visual field

Open angle glaucoma is a chronic, progressive disease of multifactorial genesis. Together with intraocular pressure increase and lesions of the optic nerve head it is manifested mainly by changes in the visual field, leading to complete blindness in the terminal phase (1, 2).

The etiopathogenesis of the disease is still not completely clear, and none of the present-day theories (vascular, axonal transport blockade, mechanical) has satisfactorily explained the nature of lesions due to open angle glaucoma (2–8). As early as in 1977 *Drance* (9) brought up a still actual question of whether an increase in intraocular pressure

is a sign of initial mechanical blockage of axonal transport, or whether it develops secondarily, as a consequence of ischaemia. Since circulation problems are involved in all those theories, it seems reasonable to consider the circulation theory to be the most acceptable one.

Regulation of increased intraocular pressure can be achieved by drugs and thus, at least partially, the progression of disease can be stopped. In younger patients, in the initial phase of the disease, while the neuron lesions are still functional, intraocular pressure reduction could be leading to the regression of the disease, while in older patients, regardless of decreased intraocular pressure, visual field defects frequently tend to progress (10, 11). Quite recently, a new, effective method has been introduced for the treatment of visual field defects caused by open angle glaucoma by hyperbaric oxygen (12, 13). The method makes use of hyperbaric chambers in which patients breathe 100% oxygen at a pressure greater than 1.0 bar (hyperbaric oxygen). The widely accepted name for the method is hyperbaric oxygenation.

The basis for the therapeutic effect of hyperbaric oxygenation is provided by an increase in oxygen transport capacity in body fluids (higher than tenfold), enabling a very fast, practically instantaneous, correction of hypoxia. Besides this elementary mechanism showing effects during hyperbaric oxygenation, it should be emphasized that there are important late effects, showing after hyperbaric oxygenation, some of them lasting for several months, which are also useful for correcting hypoxia (14–17).

Pressure and exposure time (dose) are drastically limited by the toxic effects of hyperbaric oxygen. That fact accounts for the existence of various hyperbaric oxygenation protocols that are result more of clinical impressions than of research-based experience (14, 16).

National and international societies have their own lists of approved uses of hyperbaric oxygenation (18). Apparently, however, there are not many indications for ophthalmological diseases on current lists (18, 19). This may be due to precaution, since marked, possibly negative effects of hyperbaric oxygenation on circulation and on structures of the central nervous system could be expected, therefore also on the organ of vision (14–17, 20). However, there are reports on some eye diseases, glaucoma among them (12, 13), being successfully treated by hyperbaric oxygenation (17, 20, 21).

The dominant vascular theory and some improvements of vision in patients having open angle glaucoma, who had been treated by hyperbaric oxygenation for peripheral vascular diseases at the Department of Underwater and Hyperbaric Medicine, encouraged us to apply hyperbaric oxygenation in the treatment of open angle glaucoma in 1986. Soon after that, in 1988, in the first prospective, placebo-controlled, double-blind clinical study on the effects of hyperbaric oxygenation on open angle glaucoma, *Bojić and coworkers* reported that hyperbaric oxygenation significantly increased visual field findings ($P<0.01$), and had no effect on intraocular pressure (13).

Encouraged by these results, we continued a double-blind clinical study on the effects of hyperbaric oxygenation on open angle glaucoma, with a dose of choice as a hall-mark.

PATIENTS AND METHODS

The subjects in the study were 111 patients with a diagnosis of open angle glaucoma, mean age 56.9±6.4 years. None of the patients had undergone a surgical treatment of open angle glaucoma. Their intraocular pressure was drug regulated. No contraindications for hyperbaric oxygenation were present. The patients were all briefed about the study and signed an agreement consenting to participate. Two groups were formed at random: a control group (20 patients) and an experimental group (91 patients).

For hyperbaric oxygenation served a large walk-in recompression chamber at the Department of Underwater and Hyperbaric Medicine, with 10 built-in-breathing-system units SAA-I Dräger. Eight units were adjusted for 100% oxygen breathing for the experimental group and two for Nitrox-10.5 placebo mixture breathing, providing for the control group normal oxygen conditions at the pressure applied. Both groups breathed their mixture five days a week, once a day for 90 minutes with a five minute air-break in the middle, at a pressure of 2.0 bars.

Control patients were exposed to hyperbaric placebo treatment in a 30-session course. The patients in the experimental group were randomly classified into four subgroups and exposed to a hyperbaric oxygenation course of 30 sessions (31 patients), 20 sessions (20 patients), 15 sessions (20 patients) and 10 sessions (20 patients).

All the patients were examined by an ophthalmologist. The examination included the determination of visual acuity by standard methods, of intraocular pressure by the method of applanation tonometry using biomicroscope Haag-Streit 900, and of visual field by quantitative kinetic perimetry after Goldman using a Marc 2000 perimeter. The visual field areas obtained in that way were digitalized by a Calcomp 9000 digitizer and converted to square centimetres by a Digital PDP-11/75 computer. The results obtained were compared with »normal« results, represented by those of a group of 29 healthy, young soldiers, mean age 21.5 years, with normal neurological and ophthalmological findings. Visual field and intraocular pressure values were determined in the patients before and after hyperbaric exposure, as well as at control examinations after three and six months.

Standard methods and computer software support were used for statistical analysis.

RESULTS

During the follow-up, no changes in visual acuity were noted either in the experimental or in the control group. In the experimental group the mean intraocular pressure values were 17.2 mmHg before treatment and 17.1 mmHg after hyperbaric exposure showing no statistically significant differences. In the control group the mean intraocular pressure

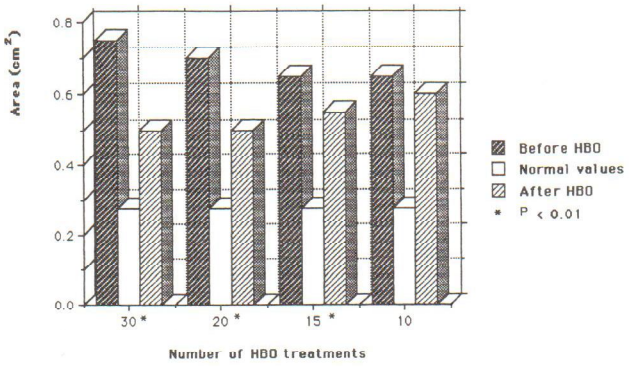

Figure 1. *The blind spot area in the experimental group before and after hyperbaric oxygenation treatment*

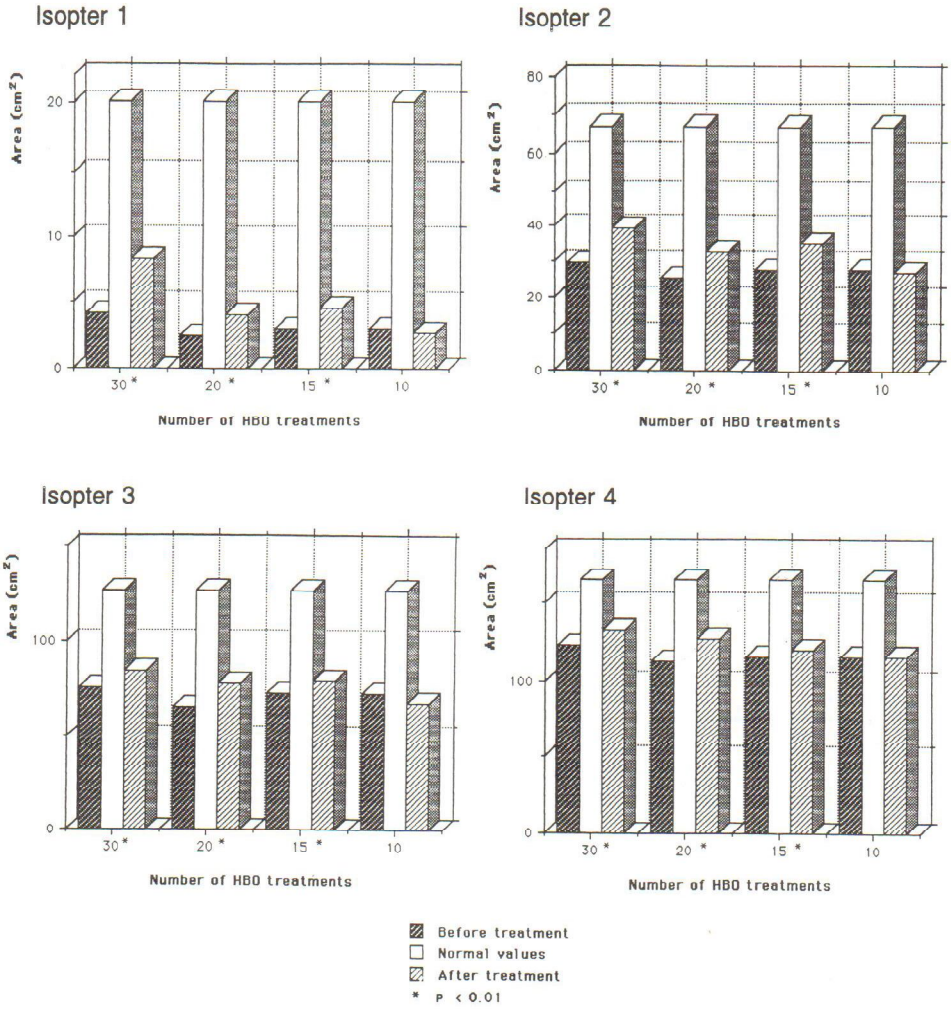

Figure 2–5. *Isopter 1, 2, 3, 4 areas in the experimental group before and after hyperbaric oxygenation treatment*

before treatment was 16.9 mmHg and after treatment 16.7 mmHg. The values did not differ when measured after three and six months.

Figures 1–5 show the mean blind spot areas and isopters (I-1 to I- 4) for the experimental group before and after the 30, 20, 15 and 10 hyperbaric oxygenation session courses, in comparison with normal values.

Comparison of the visual field values before and after hyperbaric oxygenation with normal values in respect to the number of course sessions shows that the blind spot

area decreased by 78.5% in the 30-session course, 68.5% in the 20-session course, 39.5% in the 15-session course and by 8.5% in the 10-session course. At the same time, the areas within isopters I-1 to I-3 increased: in the 30-session course from 20.5 to 6.5%, in the 20-session course from 9.0 to 8.0% and in the 15-session course from 7.5 to 5.0%. In the 10-session course (I-4) slight lowering of values, from -0.6 to -5.8%, was noted. The effectiveness level was the most prominent in the blind spot area, decreasing peripherally. It was also noted that the level of effectiveness was inversely proportional to the development of the scotoma area as indication of the severity of the disease, and directly proportional to the number of sessions.

The increase in the visual field area was statistically significant at the level of $P<0.01$ in the 30-, 20- and 15-session courses, whereas no significance was established in the 10-session course.

Comparison of the visual field areas before and after hyperbaric oxygenation to normal values and the number of course sessions gave the following ranges of correlation levels: for the blind spot from 0.20 to 0.96 and for isopters from -0.24 to +0.95. Regarding hyperbaric oxygenation courses that showed statistically significant differences, an average correlation level was the highest for the 20-session course, ranging from 0.86 for isopter I-3 to 0.89 for the blind spot.

During the follow-up, changes in the visual field in control patients were discrete and statistically not significant (Figure 6). In the experimental group, the visual field values taken immediately after hyperbaric oxygenation treatment had the same level of statistical significance as the control values measured at the end of three months. After six months the values decreased from 48 to 55%. The decrease was the most prominent in the blind spot area.

Immediately after hyperbaric oxygenation, as well as at later controls in both groups, a slight depression was noted in two patients (1.8%) regarding the blind spot, and in nine patients (8.1%) regarding peripheral isopters.

Mainly after longer courses, in nine presbyopic patients an improvement of short vision was noted, ranging from -0.5 to -1.5 dpt. At the controls within three months this effect was no longer present. No other ocular side-effects were noted.

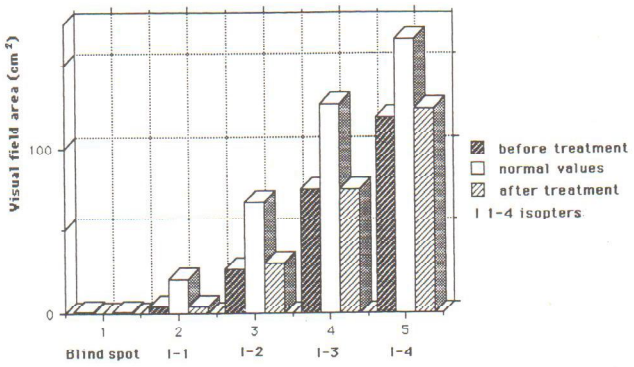

Figure 6. *Visual fields in the control group before and after hyperbaric oxygen treatment*

DISCUSSION

In general, the method of hyperbaric oxygenation is rarely applied in the treatment of eye diseases, especially when the management of open angle glaucoma is concerned. We have found only two relevant reports in literature (12, 13).

In 1978 *Andreyev and co-workers* applied hyperbaric oxygenation in treating 13 patients with open angle glaucoma. They used pressures from 1.5 to 3.0 bars, once a day, up to 15 sessions in total. In about half of their patients they observed moderate amelioration of the visual field and visual acuity (12).

In this study we have found no effect of hyperbaric oxygenation on visual acuity and intraocular pressure in patients with open angle glaucoma. *Lyne* reported in 1978 that hyperbaric oxygenation treatment of patients with diseases of the eye, among whom there were no patients with glaucoma, caused no changes in intraocular pressure (22). *Gallin and co-workers* however, found a decrease in intraocular pressure values in their group of patients treated by hyperbaric oxygenation (23).

In our control patients there were practically no changes in visual field areas. That suggests that hyperbaric treatment alone, without hyperbaric oxygen, had no effect on the vision in patients with open angle glaucoma. On the other hand, hyperbaric oxygenation caused a significant increase in visual field values in the experimental group. This is in agreement with the findings of *Andreyev and co-workers* concerning the beneficial effects of hyperbaric oxygenation in the treatment of glaucomatous lesions of the visual field (12). Unfortunately, as the authors failed to provide detailed numerical data about the level of improvement achieved, we have been unable to compare the results. The level of improvement in our patients was inversely proportional to the distance from the blind spot and to the disease severity, while directly proportional to the number of hyperbaric oxygenation sessions.

With the 10-session course no satisfactory results were obtained, there was no statistically significant difference, and the correlation level was low. The effectiveness and the correlation level increased with the course length. Statistically significant differences ($P<0.01$) were noted immediately after hyperbaric oxygenation treatment in the other courses as well as at the control examination three months later. The best results were achieved with the 30-session course. The most rational relationship between the results and the course length was found in the 20-session group, which had the highest average correlation level, suggesting that in an initial treatment a course of 20 hyperbaric oxygenation sessions should be applied.

At the control examination six months after the treatment, statistical significance was no longer present with any of the courses, showing that the disease was not cured, and that hyperbaric oxygenation treatment should be repeated if the effect is to be preserved.

Vascular theory supporters, like *Hayrech and co-workers* (7), think that visual field lesions are a result of vascular insufficiency of peripapillary chorioidea and nutritive capillaries of the optic nerve head.

Our results confirmed a statistically significant and more beneficial effect of hyperbaric oxygenation on the visual field in patients with open angle glaucoma, in comparison with classical treatment by drugs. Vascular theory is indirectly supported by the localization, dynamics, level of increase and regression of the visual field. It is very probable that, in a low-perfusion capillary network, changes in nerve cells sensibility are of functional nature, thus reacting well to hyperbaric oxygenation. However, in the case of a perfusion neuronal damage is final, therefore visual field loss permanent.

Rich oxygenation acting practically instantaneously during a hyperbaric oxygenation session, oedema reduction, stabilization of connective complexes of the interendothelial tissue, improvement of rheological blood properties and an increased level of antioxidant defense system showing after hyperbaric oxygenation, are the major mechanisms of hyperbaric oxygenation action in general (14). In the management of visual field lesions in patients with open angle glaucoma, those mechanisms act more efficiently than the classical drug therapy. The kind, frequency and level of the depression noted, as well as its distribution in groups, allow to conclude that it is not a matter of hyperbaric oxygenation effects, but merely a natural course of the disease.

Hyperoxic myopia is the most frequent side-effect of hyperbaric oxygenation therapy. It is a transient and relatively benign result of hyperbaric oxygenation action on lens, causing changes in its diameter (24). Because of that and because of other possible ocular side- effects, certain authors advocate extreme cautiousness when applying hyperbaric oxygenation in general (25). Its incidence and duration in our patients were the same as reported earlier by *Anderson* (24). The fact that no other serious side-effects have been registered, suggests that hyperbaric oxygenation should be applied with more optimism when side-effects are concerned.

CONCLUSION

The results of this study have confirmed those of our earlier investigation (13). They allow to conclude that in comparison with classical drug therapy hyperbaric oxygenation significantly ($P<0.01$) ameliorates the visual field in patients with open angle glaucoma, while having practically no effect on intraocular pressure.

The increase in the visual field was directly proportional to the number of hyperbaric oxygenation sessions. The best results were achieved with the 30-session »dose«. However, the results obtained after the 20-session course did not show much difference. That is why we consider the 20-session course to be a rational dose for the initial treatment.

Six months after hyperbaric oxygenation, beneficial effects were still registered, but statistical significance was lower suggesting the necessity of repeating hyperbaric oxygenation.

REFERENCES

1. *Vojniković B.* Definition and classification of glaucoma disease. (In Croatian.) In: Kilman A, ed. Primarni glaukom. Pula: Istarska naklada, 1984;185–96.
2. *Duke-Elder S, Barric J.* Glaucoma and hypotony. In: Duke-Elder S, ed. System of ophthalmology. Volume XI. Disease of lens and vitreous. Glaucoma and hypotony. London: Henry Kimpton, 1976;379–91.
3. *Anderson DR.* Is ischemia the villain in glaucomatous cupping and atrophy? In: Brochurst RJ, Boruchof SA, Hutchinson BI, Lessell S, eds. Controversy in ophthalmology. Philadelphia: WB Saunders, 1977;312–9.
4. *Radius RL.* Anatomy of the optic nerve head and glaucomatous optic nerve head and glaucomatous optic neuropathy. Surv Ophthalmol 1987;32:35–44.
5. *Quigley AH, Addicks EM, Green RW, Maumenee AE.* Optic nerve damage in human glaucoma. Arch Ophthalmol 1981;99:635–49.
6. *Anderson DR, Hendrickson A.* The effect of intraocular pressure on rapid axonal transport in the monkey optic nerve. Invest Ophthalmol Vis Sci 1974;13:771–83.
7. *Hayrech SS, Revie HS, Edwards J.* Vasogenic origin of visual fields defects and optic nerve change in glaucoma. Br J Ophthalmol 1970;54:461–72.

8. *Phelps CD.* The pathogenesis of optic nerve damage in glaucoma. A review of the vascular hypothesis. In: Blodi F, ed. Current concepts in ophthalmology. St. Louis: CV Mosby, 1972; 142.
9. *Drance US.* Is ischemia the villain in glaucomatous cupping and atrophy? In: Brochurst RJ, Boruchof SA, Hutchinson BI, Lessell S, eds. Controversy in ophthalmology. Philadelphia: WB Saunders, 1977;292.
10. *Greenidge VC, Spaeth GL, Traverso CE.* Change in appearance of the optic disc associated with lowering of intraocular pressure. Ophthalmology 1985;92:897-903.
11. *Schwartz HA, Takamoto T, Nagin P.* Measurements of reversibility of optic disc cupping and pallor in ocular hypertension and glaucoma. Ophthalmology 1985;92:1396-407.
12. *Andreyev GN, Dambite GR, Akere BA, et al.* The usage of individual clinical system on hyperbaric oxygenation in a complex treatment of some eye diseases. Ophthalmol Zh 1978;33:191-5.
13. *Bojić L, Kovačević H, Gošović S, Denoble P.* The effect of hyperbaric oxygen on glaucoma: A prospective study. In: Bakker DJ, Schmutz J, ed. Hyperbaric medicine proceedings. Basel: Foundation for hyperbaric medicine, 1990;273-8.
14. *Kovačević H.* Clinical application of hyperbaric oxygen. (In Croatian.) In: Agolli B, ed. Pomorska medicina V (Naučne rasprave). Beograd: Mornarički glasnik, 1990;375-87.
15. *Davis JC, Thomas TK, ed.* Hyperbaric oxygen therapy. Bethesda (MD): UMS, 1977.
16. *Davis JC, Thomas TK, ed.* Problem wounds - The role of oxygen. New York-Amsterdam-London: Elsevier, 1988.
17. *Fischer B, Jain KK, Braun E, Lehrl S.* Handbook of hyperbaric oxygen therapy. Berlin-Heidelberg: Springer-Verlag, 1988.
18. *Anonymous.* World's indications for hyperbaric oxygen therapy. Annals of Hyperbaric Medicine 1988;1:49-65.
19. *Mader JT, ed.* Hyperbaric oxygen therapy - A committee report. Bethesda (MD): UHMS, 1989.
20. *Jain KK.* Textbook of hyperbaric medicine. Toronto-Lewiston (NY)- Bern-Gottingen-Stuttgart: Hogrefe-Huber, 1990.
21. *Bojić L, Bračić V, Kovačević H, Denoble P.* Our experience in the usage of hyperbaric oxygen in ophthalmology. (In Croatian.) In: Agolli B, ed. Pomorska medicina V (Naučne rasprave). Beograd: Mornarički glasnik, 1990;393-7.
22. *Lyne HJ.* Ocular effects of hyperbaric oxygen. Trans Ophthalmol Soc UK 1978;98:66-8.
23. *Gallin P, Podos S, Yablonski M.* The effect of increased oxygen on intraocular pressure of human eyes. Invest Ophthalmol Vis Sci 1978;31(Suppl):144-51.
24. *Anderson B, Former JC.* Hyperoxyc myopia. Trans Am Ophthalmol Soc 1978;76:116-24.
25. *Kopferschmitt J, Sauder PH, Jaeger A, Mantz JM.* Iatrogenic ophthalmological effects of HBO - A case involving multiple sclerosis. In: Bakker DJ, Schmutz J, ed. Hyperbaric medicine proceedings. Basel: Foundation for hyperbaric medicine, 1990;269-72.

Sažetak

IZBOR DOZE HIPERBARIČKOG KISIKA U LIJEČENJU GLAUKOMA

Istraživanje je obuhvatilo 111 bolesnika s glaukomom otvorenog kuta, podijeljenih u kontrolnu skupinu (20 bolesnika) i eksperimentalnu skupinu (91 bolesnik) s četiri podskupine za hiperbaričku oksigenaciju: od 30 seansi (31 bolesnik), 20 seansi (20 bolesnika), 15 seansi (20 bolesnika) i 10 seansi (20 bolesnika). Upotrijebljena je višemjesna stacionarna rekompresijska komora jednom na dan, na tlaku od 2,0 bara tijekom 90 minuta. Vidna oštrina i prosječna vrijednost intraokularnog tlaka prije i nakon hiperbaričkog tretmana nisu se statistički značajno razlikovale ni kod jedne skupine, što se održalo i na kontrolnim pregledima nakon tri i šest mjeseci. Tijekom razdoblja praćenja promjene površine vidnog polja bolesnika kontrolne skupine bile su diskretne i bez statističke značajnosti. U isto vrijeme povećale su se površine vidnog polja bolesnika eksperimentalne skupine nakon hiperbaričke oksigenacije u svim podskupinama. U seriji od 10 seansi hiperbaričke oksigenacije, povećanje vidnog polja nije bilo statistički značajno. U ostalim serijama hiperbaričke oksigenacije, statistička značajnost bila je na nivou $P<0,01$. Na kontrolnim pregledima nakon tri mjeseca očuvao se isti nivo statističke značajnosti, koji je nestao na pregledima nakon šest mjeseci. Preporučuje se u inicijalnom

liječenju provesti niz od 20 seansi hiperbaričke oksigenacije. Kada vrijednosti vidnog polja opadnu na oko 50% poboljšanja postignutog u inicijalnom tretmanu, sugerira se ponavljanje hiperbaričke oksigenacije.

Očni odjel Nove bolnice, Split [1], Odjel za podvodnu i hiperbaričku medicinu Instituta pomorske medicine, Split [2], Hrvatska

Ključne riječi: glaukom otvorenog kuta, hiperbarička oksigenacija, intraokularni tlak, vidno polje