SUBMACULAR HEMORRHAGE FOLLOWING PHOTODYNAMIC THERAPY IN THE TREATMENT OF CHOROIDAL NEOVASCULARIZATION

HEMORRAGIA SUBMACULAR TRAS TERAPIA FOTODINÁMICA EN EL TRATAMIENTO DE LA NEOVASCULARIZACIÓN COROIDEA

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ABSTRACT

Purpose: To describe the incidence, clinical features and evolution of submacular hemorrhage (SMH) occurring after photodynamic therapy (PDT) with verteporfin in the treatment of choroidal neovascularization (CNV).

Methods: A retrospective analysis of the patients treated with PDT in our hospital between July 2002 and May 2005 was undertaken.

Results: 8 out of 504 eyes treated with PDT (1.58%) developed SMH; 4 of them (0.79%) required surgical attack. The incidence of SMH for every application of PDT was 0.65% (8/1221).

The underlying disorder defined was age-related macular degeneration (AMD) in 7 cases (87.5%), and high myopia in one case (12.5%). Regarding the type of lesion, 5 were occult (62.5%; p=0.01), 1 predominantly classic, 1 minimally classic, and the last one was not classified. The average final visual acuity (VA) was 0.057, with 25% of patients having a VA ≥ 0.1. Patients lost 4 Snellen lines on average.

Conclusions: SMH after PDT was an event of unknown etiology and low frequency. The incidence in

RESUMEN

Objetivo: Describir la incidencia, características clínicas y evolución de los pacientes que desarrollaron hemorragia submacular (HSM) tras terapia fotodinámica con verteporfin (TFD) en el tratamiento de la neovascularización coroidea (NVC).


Resultados: 8 de 504 ojos tratados con TFD (1,58%), desarrollaron HSM, de los cuales cuatro (0,79%) precisaron intervención quirúrgica. La incidencia por aplicación de TFD es de 0,65% (8/1221).

En siete de los ocho casos (87,5%) la patología de base fue la degeneración macular asociada a la edad (DMAE), y en un caso (12,5%) la miopía magna. Respecto a la composición de la lesión, cinco eran occultas (62,5%; p=0,01), una predominantemente clásica, una mínimamente clásica, otra no valorable. La AV final media era de 0,057, siendo ≥ 0,1 en 25% (2/8), con una pérdida media de 4 líneas de Snellen.
our series (1.58%) was comparable with that described in the world literature (0.24-9.0%). The greatest incidence of AMD was in the occult group with no classic type of CNV, suggesting a possible higher risk for SMH in this type of lesion. It is mandatory to inform patients of the possibility of this complication, which can compromise the visual result of the PDT, and sometimes require surgery. The low risk of SMH related to the PDT justifies its application when it is indicated (Arch Soc Esp Oftalmol 2006; 81: 685-692).

Key words: Submacular hemorrhage, age-related macular degeneration, photodynamic therapy, verteporfin, choroidal neovascularization.

INTRODUCTION

Photodynamic therapy (PDT) with verteporfin has proved to effectively and safely reduce severe and slight visual loss risk in selected patients with subfoveal choroidal neovascularization (CNV) secondary to Age Related Macular Degeneration (ARMD) and pathological myopia (TAP and VIP studies) (1-4). However, both studies reported occasional cases of acute and severe visual acuity (VA) loss (at least 20 letters) within the first seven days after treatment (TTO). Their conclusion is that the severe VA loss risk is low and attributable to increased subretinal fluid, delay of choroidal perfusion, subretinal or sub-pigmentary epithelium hemorrhage or without evident cause in angiofluorescein graph (AFG) (5). It has also been reported that some patients develop submacular hemorrhage (SMH), without VA reduction detectable by the patient, which can be interfere with new TTOs, affect visual result and even require surgery (6).

The purpose of this study is to describe the prevalence, clinical characteristics and evolution of SMH produced in the course of treatment with PDT in our environment.

SUBJECTS, MATERIAL AND METHODS

The study comprises 504 eyes of 470 patients (1221 PDT sessions) diagnosed with CNV secondary to ARMD and magnus myopia (MM), which began treatment with PDT between July 2002 and June 2005 in the ophthalmology service of our hospital. PDT was applied according to standard parameters [IV infusion of 6 mg/m² of verteporfin during 10 minutes (Visudyne, Novartis, Bülach, Switzerland), and application of 689 nm diode laser (Zeiss, Oberkochen, Germany), 50 J/cm² and intensity of 600 mW/cm², with an exposure time of 83 seconds.

The TTO indication was based on the criteria proposed by the TAP and VIP studies (1,3), which were modified with the appearance of new publications thereof. Accordingly, indications have widened in the course of time from the predominantly classical CNVs secondary to myopia in a
first period to concealed in non-classical CNVs. In addition, other PDT indications have been studied beyond the TAP and VIP such as CNV secondary to inflammatory pathologies, central serous choroidopathy (CSC), angioid or idiopathic stria
tions, , polypoideal CNV, retinal angiomatous pro
liferation. In these we did not find any HSM case and therefore they are not included in the statistics, which refer to ARMD and MM cases.

As regards the type of lesion, we applied the angiographic criteria of the TAP and VIP studies, classifying them as predominantly classical, minima
ly classical and concealed without classical component.

The indications for new treatments was also in accordance with the criteria of said studies, i.e., presence of contrast leakage in AFG or signs of activity such as subretinal fluid or hemorrhage not present in the previous visit.

HSM has been considered to be a hemorrhage produced in the course of TTO with PDT which involves the center of the macula and accounts for an important VA reduction and/or prevents an assessment of the characteristics of the lesion and/or the need for a new treatment.

In each visit the data collected include best cor-
corrected VA, pathology causing the TTO, angiograph
ic type of the lesion, size thereof, whether or not TTO has been received as well as side effects or complications. This data is stored in a database (Microsoft Access for Windows, version 9.0.0.2719), for subsequent statistical analysis with S.A.S. version 8.02 (from S.A.S Institute Inc., Cary, N.C., USA).

RESULTS

Eight of the 504 eyes treated for CNV secondary to ARMD or MM have exhibited HSM, with a prevalence of 1.58%. Of these, half needed vitrectomy for its displacement from the macular area, that is 0.79%. The probability of exhibiting HSM for each PDT session is of 0.65% (8/1221).

The mean age of the 8 cases was 76.75 SD 8.9 years (69-93; 72), 5 cases of 194 (2.57%) were men and 3 of 310 women (0.96%). There were no statistically significant differences in what concerns age or sex of the cases vis-à-vis the rest of the series.

Of the eight cases, 7 (87.5%) appeared in patients with ARMD, which represents a prevalence of 2% of all ARMD cases (7/349). The remaining case was myopia magna and exhibited signs of age-relat
ed maculopathy and therefore was included as a mixed lesion, with a prevalence of 0.64% (1/155) against the total treated myopic lesions (fig. 1). Out of the 8 HSM cases, three were taking oral antico
gulants and 5 were not. Likewise, one patient exhibited hypercholesterolemia, 3 had high arterial pressure and one case was in treatment for ischemic cardiopathy. The most relevant characteristics of the series are summarized in Table I.

As regards the initial clinical presentation, 5 of the 8 cases were concealed lesions, i.e., 62.5% of all hemorrhages. The rest appeared in minimally classical lesions (12.5%), in another predominantly classical (12.5%), and another one which was not assessable (12.5%) because AGF was not performed due to the patient being allergic to fluorescein (fig. 1).

The prevalence for each type of lesion was of 0.29% in predominantly classical lesions (1/344), 2.8% in minimally classical ones (1/36), and 4.7% in concealed lesions (5/105). This difference was significant after the statistical analysis, with p=0.01, that is, there was a statistically significant association between the initial lesion type and the probability of having HSM.

In 4 cases, the hemorrhage occurred after the first PDT session, in two after the second one and in 2 more after the third session.

As regards the time of appearance, two groups can be differentiated: early HSM (before ten days
after the PDT) in two cases, and late HSM (arising after 6 weeks) in 5 cases. One patient did not refer reduced vision and the hemorrhage was a finding of the re-treatment visit. These two groups also had differentiating characteristics:

Early HSM, central, small size (figs. 2 and 3).

Late HSM (after 6 weeks, up to 3 months), peripheral to the lesion, large size, pseudo-tumoral (figs. 1, 4 and 5).

In what concerns VA, the initial value was 0.28 (average) and went to 0.057 at the end of the follow-up. This involved a mean loss of 4 Snellen lines (fig. 6). Only one patient maintained VA, while the rest lost vision. Two patients (25%) had a VA ≥0.1 at the end of the follow-up (one predominantly classical and minimally classical lesion), whereas the six remaining ones (75%) the VA was < 0.1.

The mean final VA of the different groups of lesions are seen in Fig. 7. It can be seen that the final mean VA of HSM cases (0.05) is lower than the final mean VA of ARMD cases (0.15), and lower than the final mean VA of concealed lesions (0.30).

As regards the size of the lesion, it went from 4,000 to 10,000 microns mean size (GLD), multiplying by 2.6 (fig. 8). The early HSM hardly increased the size of the lesion. However, all the late HSM increased up to 6 times bigger than the initial GLD.

Finally, 4 cases required surgery for displacing the hemorrhage, three of which appeared in concealed lesions and the fourth in a non-assessable lesion. These patients also associated low visual acuity values (≤0.05) (table I).

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<th>Initial VA</th>
<th>Final VA</th>
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<th>Time</th>
<th>N° of TFD</th>
<th>Vitrectomy</th>
<th>ACO</th>
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Table I. Relevant demographic and clinical characteristics of the series

PC. Predominantly classical lesion. MC: minimally classical lesion; O: concealed lesion; ACO Oral anticoagulant administered.

Figs. 2 and 3: Concealed lesion with associated hemorrhage, which developed a central HSM 9 days after the first PDT. Final VA: 0.05.
DISCUSSION

The TAP and VIP studies have proved that, as compared to placebo, PDT significantly reduces the risk of VA loss in patient selected with subfoveal CNV secondary to ARMD and MM. Report #3 of said studies analyze the causes of severe VA loss after PDT. In one patient (1/402) of the TAP study, and in 3 (3/225) of the VIP Study, said cause was HSM, which represents a prevalence of 0.24% and 1.33% respectively (5). The prevalence in other studies is variable and ranges between 1.86% and 9% (6-8).

Said prevalence rates cannot be compared to that found in this study due to methodological differences. In other works a systematic and protocolized study was made of patients and, in addition, not all studies agreed about the best time to detect said hemorrhages and therefore the time for analyzing this prevalence is different in each study. In our case, we have analyzed the patients who came to

Figs. 4 and 5: Concealed CNV which developed HSM after the third PDT. This patient was taking Sintrom Final VA: 0.02.

Fig. 6: Initial and final VA of each patient with HSM (one patient, one bar). In bold type, the initial and final mean VAs.

Fig. 7: Final mean VA comparison per lesion type.

Fig. 8: Initial and final size of each patient with HSM (GLD in microns; one patient, one bar).
the practice referring visual reduction prior to the date of re-treatment as well as those who exhibited HSM at the date of re-treatment. There is the possibility of losing patients in the follow-up either because they declined further treatment or they were not referred by their hospital on the grounds that the lesion could not be treated at that time. Accordingly, we believe that the prevalence of HSM associated to PDT is probably greater in our environment, although it cannot be determined to what extent. In any case, it is low and within the published ranges. It can also be said that it has appeared almost exclusively in patients with a diagnosis of ARMD (7 out of 8, i.e. 87.5%), because in only one HSM case the patient had myopia magna, although the lesion was classified as mixed because she exhibited signs associated to ARMD. Probably for this reason the mean age of the 8 cases is somewhat higher than that of the series and similar to that of patients with ARMD diagnostic (77.54 SD 7.22).

On the other hand, there is no study to date which analyzes this complication for all types of lesions, because in the TAP study most lesions are predominantly classical whereas in the VIP study there is a higher percentage of patients with concealed lesions. In turn, in the other studies we analyzed only one specific type of lesion has been treated (6,8) with the exception of the Theodossiadis study (7). This is the first study we know of which analyzes all patients treated for a long period of time (3 years) and which includes all types of lesions and pathologies.

In what concerns the type of lesion, we have found a considerably higher prevalence in concealed lesions (4.7%; p=0.01), which indicates that these lesions could entail a higher risk of exhibiting this complication than the rest. The prevalence in the rest of lesions is merely symbolic; besides, we cannot draw statistically significant conclusions due to the small number of cases in each group. Published studies refer to a greater prevalence of HSM in concealed lesions, although none concludes that this prevalence is statistically significant (5,6). In addition, concealed lesions comprise 3 out of the 4 cases which required surgery and exhibited a lower final VA (table I), which suggests that HSM cases associated to this type of lesion would have a worse visual prognosis than the rest.

Comparing the final VA of the cases which exhibited HSM (0.05) with the mean value of CNV secondary to ARMD (0.15), it is clearly lower (fig. 7). Accordingly, these patients lost more VA than those who did not exhibit said complication. At any rate, the final VA of the patients who exhibited severe acute VA loss in the TAP and VIP studies was similar to that of the placebo group (5), which means that their condition would not have been worse if they hadn't been treated.

As regards the number of administered PDTs, there seems to be no relationship with this variable: in 4 cases, HSM occurred after the first DPT, in 2 after the second and in a further 2 after the third. Neither did we find relationship with the administration of ACO (table I).

The etiological role of PDT in the production of these hemorrhages is controversial. The article by Theodossiadis et al (7) states that the hemorrhages related to PDT appeared within 48 hours after the application thereof and had an extremely large final size, >12,000 microns, leading the authors to conclude that they are not a part of the natural evolution of CNV. However, HSM also occurred during the natural evolution of CNVs. Thus, the TAP 1 study presented intra- and subretinal hemorrhages in 46% of the placebo group and in 29% of the group treated with verteporfin (1). These hemorrhages did not relate in time with PDT and it was suggested that they could have been due to tearing of the pigmented epithelium. On the other hand, in a series of concealed lesions Bressler et al stated that the probability of exhibiting HSM is greater after 2-3 months post-PDT (6).

After the above considerations, it would seem logical to think that if an HSM occurs soon after PDT (between 48 hours and 7 days), it could be a direct consequence of the PDT, secondary to selective vascular photothrombosis, inflammatory response, vasculitis and dysfunction of vascular barriers caused by the PDT. In addition, if the HSM is massive, it is not likely it will be part of the natural evolution of the CNV secondary to ARMD (1).

However, it cannot be said either that if the HSM is late it is not secondary to PDT, because it is known that the CNV thrombosis is reversible and that after 1 week there is a recovery of the choriocapilar circulation with repercussion in and growth of the CNV. In addition, the PDT also causes hypoperfusion of the healthy choroids and choriocapillaries surrounding the lesion, which stimulates the production of VEGF which in turns causes the growth of CNV in the periphery (9). These two
effects inherent to PDT could explain the belated HSM which, as seen in our series, are bigger and peripherally located.

In any case, no conclusions can be drawn about the etiological role of PDT in HSM caused in the course of treatment of ARMD or other pathologies.

By way of final conclusion, we believe that patients should be informed of the possibility of a moderate or severe VA reduction associated to HSM in the course of TTO with PDT which may require surgery, and that this risk is considerably greater in ARMD and hidden lesions. At any rate, we consider that the low risk of HSM in relation to PDT is not a contraindication for TTO when indicated. Additional studies are needed to establish the true prevalence of this event as well as to clarify the etiological role of PDT therein.

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REFERENCES


