OUTCOMES OF MACULAR HOLE SURGERY USING THREE DIFFERENT SURGICAL TECHNIQUES

RESULTADOS DE LA CIRUGÍA DEL AGUJERO MACULAR CON DIFERENTES TÉCNICAS DE TRATAMIENTO

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ABSTRACT

Purpose: To compare the effectiveness, efficiency and complications of three different surgical techniques employed for the treatment of macular holes between 1998-2004 in our health care centre.

Methods: A retrospective, comparative, and non-randomized study of 131 eyes with macular holes, stage III and IV, treated with three different surgical techniques was performed. Vitrectomy was performed in 25 eyes (group 1). Vitrectomy was associated with internal limiting membrane peeling in 19 eyes (group 2), and in the remaining 87 eyes, the peeling of the retinal internal limiting membrane was assisted with indocyanine green (ICG) (group 3). The concentrations of ICG used were 5%, 2.5% and 0.5%. We compared the anatomic and functional results, and the complications which occurred.

Results: The overall anatomic success rate was 88.4% (114 eyes), and it was higher in group 3 (90.6%). A visual acuity improvement was achieved in 63.6% of eyes; however there were no significant differences between the groups studied. The most important complications included cataracts (51.9%), increase in intra-ocular pressure (37.2%), retinal detachment (7.8%) and retinal pigment epithelial changes (7%). These pigment epithelial changes were associated with the use of ICG-assisted peeling (p<0.05), but there was no correlation between the changes and the concentration of ICG.

RESUMEN

Objetivo: Comparar la efectividad, eficiencia y complicaciones de las tres técnicas quirúrgicas empleadas en el tratamiento del agujero macular en el período 1998-2004 en nuestro centro.

Métodos: Estudio retrospectivo, comparativo, intervencionista y no aleatorizado de 131 ojos con agujero macular idiopático en estadío III y IV, operados con tres técnicas. En 25 ojos se realizó vitrectomía simple (grupo 1), en 19 ojos se asoció rexis de la membrana limitante interna (MLI) (grupo 2), y en 87 ojos esta rexis se llevó a cabo previa tinción con verde de indocianina (ICG) (grupo 3). Las concentraciones de ICG empleadas fueron del 5%, 2,5% y 0,5%. Se compararon la recuperación anatómica y funcional y las complicaciones en los distintos grupos.

Resultados: El 88,4% (114 ojos) lograron la resolución anatómica, siendo superior en el grupo 3 (90,6%). La recuperación funcional se consiguió en el 63,6%. En ambos casos no existieron diferencias entre grupos. Las complicaciones más importantes fueron: cataratas post-cirugía (51,9%), aumento de PIO (37,2%), desprendimientos de retina (7,8%) y alteraciones del epitelio pigmentario (7%). Esta última se relacionó con el uso de ICG (p<0,05), sin encontrarse diferencias en las concentraciones empleadas. El tamaño del agujero tuvo una correlación inversa con la agudeza visual (AV) inicial y post-qui-
employed. The hole size had an inverse correlation with initial and final visual acuity. An epi-retinal membrane was associated with better visual acuities and higher anatomic success.

**Conclusions:** In our experience, the use of ICG-assisted internal limiting membrane peeling in macular hole surgery improves the anatomic success, but may lead to retinal pigment epithelial changes (*Arch Soc Esp Oftalmol* 2006; 81: 581-590).

**Key Words:** Macular hole, vitrectomy, internal limiting membrane peeling, indocyanine green.

### INTRODUCTION

Idiopathic or senile macular holes (MH) are the most frequent form of macular holes (1) and one of the leading factors in loss of central vision. Knapp described this pathology for the first time in 1869. In 1991, Kelly and Wendel reported the first successful full closure of an idiopathic macular hole by means of a vitrectomy via pars plana followed by gaseous exchange (2). Since then, surgical techniques have evolved. Adjuvant therapies were introduced in order to induce growth of glial cells (3-8). Perifoveal internal limiting membrane peeling (ILM) was performed in order to eliminate the epiretinal membrane (ERM), releasing the cytokines in charge of triggering glial proliferation, which in turn allowed for closure of the hole and more mobile margins, to finally reduce the size of MHs (7,9-12). Since the ILM is extremely thin and transparent, releasing it is not always easy, thus the use of tincture. First, indocyanine green (ICG or VID) was used (13-20). ICG-related techniques, volume and concentration varied considerably in the different series, and so far no international protocol concerning this issue has been adopted (21). Even though ICG is frequently used for ILM tincture, concern about its toxicity on the retina and the retinal pigment epithelium (RPE) has reopened the debate surrounding its use (22-27). In order to avoid toxicity, new tinctures have emerged, for example, infracyanine green (28), trypan blue (29,30) and triamcinolone (31). Now that surgery has been widely accepted to treat Stage II, III and IV macular holes, surgeons now seek new surgical techniques that may be able to maintain current rates of anatomical and functional success and reduce complications as much as possible. Thus the recommendation of a posterior vitreous detachment during vitrectomy without removing the ILM (32) or completing a reduced vitrectomy (33).

At our center, evolution of MH surgical procedures ran parallel to new discoveries in the field. The purpose of the present study was to compare the effectiveness, efficiency and complications associated with the three surgical procedures used to treat macular holes during 1998-2004 at our hospital, as well as the results obtained and the findings published in the literature.

### SUBJECTS, MATERIAL AND METHODOLOGY

A retrospective, comparative, interventionist and non-randomized study was performed on 131 eyes suffering from Stage III and IV idiopathic macular holes (according to Gass’ classification) and treated at the Hospital Universitario Central de Asturias between 1998 and 2004. Macular holes secondary to trauma were excluded, together with patients suffering from diabetic retinopathy, age-related macular or myopic degeneration, and those with a history of retinal surgery. All individuals signed an informed consent form approved by the hospital’s Ethics Committee.

Depending on the surgical technique used, eyes undergoing surgery were divided into three groups: 1, 2 and 3. Group 1 included 25 eyes subjected to a vitrectomy without detaching the ILM; of these, 8 corresponded to males and 17 to females aged from 62 to 76, and averaging 70.3 years, standard deviation (S.D.: 4.09). Visual acuity prior to surgery for this group ranged from .02 to .3, averaging .14 (S.D.: .11). Group 2 included 19 eyes treated with
the previous technique associated with ILM detach-
ment; 9 eyes belonged to men and 10 to women aged 61 to 80, averaging 72.0 years (S.D.: 4.42).
Visual acuity prior to surgery for this group ranged from .02 and .2, averaging .09 (S.D.: .11). Group 3 consisted of 87 eyes subjected to ILM rhesis previously tinctured with different ICG concentrations; 33 belonged to males and 54 to females, ages ranging from 51 and 84 years, averaging 68.9 years (S.D.: 7.77). Visual acuity before surgery ranged from .02 to .55, averaging .12 (S.D.: .11). All groups shared similar basal characteristics.

Patients included in group 3 were administered decreasing concentrations of ICG: 5.0 mg/ml (48.4%), 2.5 mg/ml (27.4%), and .5 mg/ml (24.2%), depending on the evolution of surgical techniques and scientific knowledge at the time.

Data concerning the time of evolution for macular holes was collected for 94 eyes; evolution ranged from 1 to 120 months, averaging 12.8 (S.D.: 16.8); no statistically significant differences were found among the 3 groups.

Percentages of bilateral holes were as follows: six cases in group 1 (24%); three cases in group 2 (15.8%) and twelve cases in group 3 (13.8%). In total, 21 cases (16%) evolved into bilateral macular holes.

In all cases, full ophthalmic examination was performed before and after surgery, including: assessment of visual acuity (VA) with a Snellen chart, examination of the anterior segment, ocular pressure, visualization of the eye fundus via indirect ophthalmoscopy, and biomicroscopic examination of the macula. Retinography, angiographic exam or visual field were prescribed for selected cases.

Prior to surgery, the following data were gathered: age, gender, affected eye, best corrected visual acuity, time of evolution, presence of metamorfop-
sias, condition of the eye lens, and size of the hole.

Among the 130 eyes for which the lens was analysed prior to surgery, 15 (11.5%) had undergone combined surgery, 9 during the year 2004. The surgical procedure consisted of phaco-emulsification, intra-ocular lens implant in capsular sac, followed by vitrectomy.

Surgery was always performed by the same surgeons (JCN and CGC). All patients were intervened under peribulbar anaesthesia with a mix of 5% lidocaine (B. Braun Medical S.A Bar-celona) and .76% bupivacaine (Inibsa, S.A Labo-ratorios Barcelona), plus sedation whenever necessary. All patients underwent a three port pars plana vitrectomy, followed by detachment of the vitreous cortex. Whenever present, the epi-retinal membrane (ERM) was removed with membrane tweezers. Together with a posterior pole lens, a wide field visualization system was used during surgery.

ILM rhesis was prescribed from February 2000 on. A small incision was performed on the ILM aided by vitreous-retinal tweezers. Subsequently, an approximately three diameter disk detachment of the membrane surrounding the fovea was performed via circular rhesis.

ICG was used since March 2001. Solutions were prepared by reconstituting a 25 mg vial of indocya-
nine green (ICG-PUL-SION. Medical Systems AG., Munich) with .5 ml of sterile distilled water. Once completely dissolved, 4.5 ml of balanced saline solution (BSS) were added in order to obtain a
final concentration of 5 mg/ml, and 9.5 ml of BSS for 2.5 mg/ml concentrations. In lower concentration solutions (.5 mg/ml), instead of BSS, 9.5 ml of 5% glucose solution were added. One ml of the latter solution (2.5 mg) was diluted with 4 ml of glucose solution to obtain the desired concentration. A small amount of this solution (.1-.2 ml) was placed directly on the retina at the macula level while closing the infusion. Before proceeding to washing and aspiration, two minutes elapsed in the case of 5% and 2.5% ICG, and 30 seconds for .5% concentrations.

Finally, a fluid-gas exchange took place (C3F8 or SF6—used in 17.6% of eyes—) at moderately expandable concentrations (15% and 25% respectively), and specific postural treatment was prescribed for 7 days.

All patients were assessed the day following surgery, one week later, and then after one, three and six months. Follow-up lasted up to 48 months, covering only patients who attended our health center, as all other patients were gradually referred to their respective healthcare services. Thus, follow-up periods ranged from 6 to 48 months (10.8 months on average). Visual acuity, intra-ocular pressure, eye lens condition, post- and pre-surgical complications, and macular conditions were checked.

Anatomic success was defined by the complete elimination of sub-retinal liquid and hole borders. The hole was assessed after intra-ocular gas had completely disappeared. Incomplete initial closure and reopening of the hole were both considered surgical failures.

Functional recovery was defined by any improvement of visual acuity by one or more Snellen lines.

Results were analysed with non-parametric tests where p<.05 was considered statistically significant. The statistical analysis was performed using SPSS 12.0 for Windows (SPSS for Windows, SPSS Inc, Chicago, USA).

RESULTS

One hundred and thirty-one (131) eyes were collected, 81 belonging to females (61.8%) and 50 to males (38.2%), ages averaging 69.6 years (51 to 84 year interval). Sixteen percent (16%) of patients exhibited bilateral macular holes during follow-up. Depending on the groups, bilateral holes were distributed as follows: 6 cases in group 1 (24%); 3 cases in group 2 (15.8%) and 12 cases in group 3 (13.8%).

Anatomical success was assessed for 129 eyes. Of these, in 16 cases (12.2%) the first surgical procedure had failed. Half of them (6.1%) underwent a second surgery. Anatomical success was achieved in 114 eyes (88.4%). When analysing results by groups, we found anatomical resolution in 80% (20 cases) of patients from group 1; 89.5% (17 cases) of patients from group 2; and 90.6% (77 cases) of patients from group 3. Despite increased success, no significant differences were appreciated among groups in terms of resolution percentages. Functional recovery and improved visual acuity by one or more lines were achieved in 82 cases (63.6%); 26 eyes (20.3%) retained the same visual acuity as before surgery; and 20 grew worse (15.6%) (fig. 3). No statistically significant differences were found either among groups (fig. 4).

Complications derived from surgery included two retina detachments (RD) during surgery caused by small peripheral ruptures close to the sclerectomies; two cases of persistent central scotoma after surgery; one case of gas leaking into the anterior chamber during exchange; and four cases of RD several weeks after surgery. No subgroup analysis was performed, as the occurrence or absence of complications was studied in only eight patients from groups 1 and 2. The few complications observed did not imply their absence in these two groups nor their accumulation in group 3, but rather a less accurate clinical data collection from patients’ history collected during check-up in the first few years, with the subsequent loss of information.

51.9% of the eyes intervened revealed post-surgical cataracts; no differences were found among these groups. During the first check-up after surgery, 29 eyes (37.2%) showed higher intra-ocular pressure (IOP). In all cases, it disappeared in the first 3 weeks. No differences were observed among these groups, nor were they found through the multivariate analysis on the gas used for tamponade and the presence of high IOP after surgery. Nine eyes (7%) belonging exclusively to group 3 exhibited alteration of the retinal pigment epithelium, a statistically significant result (p<.05).

Nonetheless, it was impossible to determine whether alterations were due exclusively to tincture of the ILM with ICG—direct toxicity— or to the
combination of rhesis and tincture, as significant differences could only be found comparing the use or not of ICG (tables I and II). In other words, the three most frequent complications after macular hole surgery were cataracts (51.9%), high IOP (37.2%), and RD during surgery or several weeks after surgery (6 eyes –7.8%–); the only statistically significant variable was RPE alteration due to the use of ICG.

In order to identify any pre-surgical or intra-surgery predictive factors of surgical success, a second multivariate analysis was undertaken using anatomical resolution, with initial and final VA as dependent variables. An inverse correlation was found between the size of the hole, and initial and final VA (figs. 5 and 6); nevertheless, anatomical success was not related to size (p=.56). Regarding time of evolution for macular holes, the longer the time, the higher the number of failures (the average time of evolution for open holes was 19.20 months, 11.98 months for closed holes), but SD varied greatly in both groups (21.27 and 16.41, respectively) and the

<table>
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<th>TYPE SURGERY</th>
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<tr>
<td></td>
<td>Count (%)</td>
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* Likelihood ratio: .020.
The presence of ERM was correlated to improved pre-surgical (an average .18 versus .11 without ERM) and post-surgical (average .33 versus .20 without ERM) visual acuity, as well as a greater anatomical success (100% versus 86.5%). Nevertheless, no statistical survey has proven to be significant, possibly due to the insufficient size of the sample.

Lastly, the impact of the different ICG percentages used in ILM tincture on the results obtained was analysed. No differences were found among the different groups between final VA (p=.32) nor anatomical success (p=.77). The group showing the highest number of complications was administered 5% concentrations (eight eyes) as opposed to the remaining six eyes, for which 2.5% concentrations were used, one receiving a .5% concentration; no significant differences were observed among them. No differences were found regarding the emergence of RPE alterations based on the different ICG concentrations used.

**Table II. Contingency Table: Use of Indocyanine Green - RPE Alteration**

<table>
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* Fisher Exact Test: .028.

**Fig. 5: Comparing the impact caused by macular hole size.**

**Fig. 6: Comparing the impact caused by macular holes (micras), as well as pre-surgical and final VA (micras).**
DISCUSSION

MH surgery is still under debate and review in search for optimal therapy guidelines. Judging from the results obtained in the different prospective and retrospective studies, it seems that surgery is the preferred treatment for idiopathic macular holes. Nevertheless, surgery should not be prescribed for every idiopathic MH. The American Academy of Ophthalmology (34) recommends surgical treatment only in stages II, III and IV, whereas Stage I MH should be supervised regularly due to their greater rate of spontaneous closure, absence of progress, and better VA.

In the retrospective survey performed on 131 eyes in stages III and IV, global anatomical success rates amounted to 88.4% and functional success was 63.6%; values similar to the average reported in the literature (11,12,14,16,18). In our series, 20 patients grew worse (15.6%), a similar proportion to Park’s 14% (35), somewhat better than Freeman’s (36) 34%, and worse than Mester’s 0% (37) and Haritoglou’s 6% (38). We found 16% of bilateral holes, similar to Ezra’s 15.6% (39).

New discoveries related to the pathogenesis of macular holes indicate that ERM, sometimes present on the retina, does not cause MH, but it is rather a result of the body’s effort to close the hole. Contraction of this membrane increased the size of the hole (40,41). Whenever an ERM is detected, it should be eliminated during surgery in order to obtain better anatomical and functional outcomes. Our survey matched the data found in the literature concerning better final VA in patients whose ERM was removed (12,41).

Several articles have illustrated the benefits of ILM rhexis (9,10). Nonetheless, there are fewer that compare vitrectomy results with and without ILM rhexis. Castro and González (11) analyzed retrospectively 50 eyes from 48 patients presenting Stage III and IV idiopathic MHs, and found anatomical and functional improvement in the group which underwent ILM rhexis. Al-Abdulla et al (12) reported a higher rate of closure after dissecting the ILM, though found no differences in final VA. Kumagai et al (18) suggested that ILM peeling increased anatomical success and decreased recurrences; nonetheless, benefits were limited in long-standing and large MHs; and no differences were found in final VA. In the present study, no significant differences were found between both types of surgery in terms of both anatomic and functional success, although there was a greater number of closures after performing ILM rhexis (89.5%-90.6% versus 80%).

An inverse correlation was found between the size of the hole, and the initial and final VA; nevertheless, anatomical outcome was not related to size. As for the time of evolution of macular holes, there seems to be a correlation between longer evolutions and higher failure rates. These results are similar to those reported by Blumenkranz (8), who deemed anatomical and functional success as significant for subgroups of less than 450-micra and 6-month-old MHs; identical results were reported by Brooks (9). Kumagai also found that the smaller the size and the shorter the time of evolution, the more significant success rates were for the group which did not undergo ILM rhexis; the same did not apply to the group undergoing ILM rhexis. This author confirmed the efficacy of rhexis in MHs more than 6 months old and its lack of efficacy in larger MHs when taking into account the similar success rates found in both groups (18).

On the other hand, ILM rhexis may harm the underlying retina. Haritoglou et al (38) found in 56% of patients paracentral scotomas which, though asymptomatic, would indicate a lesion in the underlying retina. In the present survey, no differences were found in terms of visual field alterations for the different groups.

ICG allows for a better viewing of the ILM, which in turn facilitates surgery. Other variables under control, certain series reported a decrease in functional success when using ICG (19). Some described both anatomical and functional improvement (13,16,17,20). In the present study, no differences were observed, and in turn good surgical and functional results were obtained. Another increasingly relevant aspect related to the use of ICG is toxicity. Only one major RPE alteration was detected (7%) when using ICG. These findings agree with those reported by Engelbrecht et al (24) and Ho et al (25). Similarly, field defects (19,27) have been described as being caused by damage of the nerve fiber layer and linked to the emergence of a false cleavage plane due to ICG (22). Our series included just two patients suffering from scotomas. Only a few studies have attempted to link ICG toxicity to its concentration, pH, osmolarity or time left in contact with the retina. Kwok et al (21) found no differences when using .2% and 1.25% concentra-tions. Similarly, no differences became apparent in our
series with respect to concentrations ranging from .5% to 5%. Nevertheless, these groups should not be compared, as their time of exposure to the retina (in the case of initial surgery, exposure took 2-3 minutes, later reduced to 30 seconds) and the dissolvent used (BSS at first and currently 5% glucose solution) differed.

Van de Moere et al (28) described the use of infracyanine green as an alternative to ICG, obtaining anatomical and functional success. V ote et al (29) suggested the use of trypan blue, even though it is not a selective pigment for ILM. Lee et al (30) compared ICG and trypan blue, obtaining better visual results in the group using blue. Intra-ocular surgery with triamcinolone also proved successful in closing MHs (31).

The latest advances in MH surgery have attempted to achieve customized (32), minimally traumatic (33) procedures.

Our results were subjected to many limitations. It was a retrospective, consecutive and non randomized study on each of the 3 techniques used. In some instances, final VA values were obtained after cataract surgery, so that no assessment was made as to whether post-surgical VA was different prior and after phacoemulsification and whether the latter stresses any particular complication. Similarly, the possibilities of obtaining statistically significant results were slim due to the reduced size of samples and the unequal collection of data through time. The results obtained did nevertheless provide certain hints regarding the efficacy, efficiency and safety of the techniques employed and allow to set future action protocols regarding this pathology.

We may conclude by saying that surgery improved visual acuity in 63.6% of cases. Despite this increase, no significant differences were found regarding the percentage of anatomic and functional success among these groups. A probable cause could be the reduced size of subgroups.

The size of holes and initial VA values were used as predictive factors of surgical success. Nevertheless, anatomical resolution was more related to evolution rather than size of macular holes. The presence of ERM was linked to a better initial and final visual acuity, as well as to greater anatomical success. EPR alterations were analysed in the group subjected to ILM rhexis using ICG. Although the colorant used could be blamed for these alterations due to direct toxicity, it was not possible to determine whether the very rhexis of dyed ILMs may have contributed to their emergence, perhaps through a false cleavage plane.

Many questions remain unanswered. From a surgical point of view, it would be interesting to establish whether it is always necessary to perform ILM rhexis, clarify the real benefits associated with the use of ICG or other tinctures, and determine the etiology behind EPR alterations. From a social point of view, the real benefits of surgery on patient’s everyday life should be assessed as well.

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