Porous vs non-porous orbital implants after enucleation for uveal melanoma: a randomized study

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PRÉCIS

A randomized study comparing hydroxyapatite with acrylic orbital implants in patients who underwent enucleation for uveal melanoma showed no major long-term differences in lid position, ocular motility, complications and satisfaction.

ABSTRACT

Purpose: To compare hydroxyapatite with acrylic implants after enucleation for uveal melanoma (UM) with respect to lid position, ocular motility, implant complications and patient satisfaction.

Methods: Patients undergoing primary enucleation for UM between May 2005 to November 2012 at the Liverpool Ocular Oncology Centre (LOOC), United Kingdom, were randomized between hydroxyapatite with acrylic implants. Questionnaires were sent to patients and ocularists to comment on the main outcomes.

Results: Four hundred and sixteen patients were recruited in the study, of whom 281 were included, with 49.5% (139/281) and 50.5% (142/281) receiving a hydroxyapatite (HA) or acrylic (AC) implant respectively. Mailed questionnaires completed at ≥18 months by patients showed no significant differences between the groups in lid position, prosthetic motility, socket complications and patient satisfaction. Complications included implant extrusion (1% vs 4%), enophthalmos (26% vs 26%) and superior sulcus deformity (24% vs 24%) with HA and AC implants respectively (Fisher's exact test $P>0.0125$ in all, Bonferroni correction). Questionnaires completed by ocularists indicated no significant differences in lid opening, prosthetic motility and other complications at 6 months (Fisher's exact test, $P>0.05$ in all); there was a higher prevalence of ptosis with AC than HA implants (46% vs 25%, $P= 0.03$) and a greater need for ocularists' treatment with HA than AC (50% vs 28%, $P= 0.03$).

Conclusions: Patient-reported outcomes after enucleation for UM indicate no major differences between hydroxyapatite and acrylic implants in surgical outcomes and patient satisfaction. There was a higher prevalence of ptosis with AC and a greater need of ocularists' treatment with HA at 6 months observed by ocularists.

INTRODUCTION

Approximately 35% of patients with uveal melanoma require enucleation, either as primary treatment or because of complications following other forms of therapy.[1,2] Orbital implants inserted at the time of enucleation enhance orbital volume and improve motility of the artificial eye. Porous implants made of hydroxyapatite (HA) and non-porous implants composed of silicone or acrylic (AC) are commonly used. Porous implants allow fibrovascular ingrowth and permanent integration with orbital tissues, reportedly reducing the risk of extrusion and secondary infection.[3-5] Furthermore, they allow pegging, which enhances motility of the prosthesis.[6] They can be wrapped with different types of tissue such as donor sclera to facilitate extraocular muscle attachment, or may be unwrapped to eliminate the risk of immunologic reaction directed against the wrapping tissue and transmission of infectious disease. [6-7] Non-porous implants such as AC spheres are reported to have similar prosthetic motility in comparison with non-pegged porous implants.[8-9] They are also less costly.[6] Many studies on orbital implants have been undertaken, including one randomized study assessing implant motility.[7-17] However, most studies were retrospective and limited by small sample size or short follow-up. To our knowledge, this is the first randomized study to prospectively compare porous with non-porous orbital implants with respect to lid position, ocular motility, implant complications and patient satisfaction after enucleation as primary treatment for uveal melanoma.

METHODS

Patients were included if they underwent primary enucleation for uveal melanoma at the Liverpool Ocular Oncology Centre (LOOC) between May 2005 and November 2012.

Patients were excluded if they resided overseas, had previous eye-sparing treatments such as ruthenium plaque radiotherapy, proton beam radiotherapy or endoresection or if they had overt metastatic disease.

Pre-operatively, all patients had a full ophthalmological examination performed together with B-scan echography to assess the size of the tumour on presentation. Routine preoperative liver ultrasonography was performed if the longest basal tumour diameter was >16 mm.

Patients who were diagnosed with 'high risk' of developing metastatic disease based on the prognostic model utilized in LOOC, underwent 6- or 12- monthly liver ultrasonography or magnetic resonance imaging.[18] Detection of any metastatic disease was reported to our department. The aim of the study and the nature of different types orbital implants were explained to all participants.

All patients had consented to randomization of the orbital implant and to providing subsequent feedback following surgery by means of questionnaires. Ocularists were sent a separate questionnaire if patients consented to sharing information with them.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The service evaluation was approved by the Royal Liverpool and Broadgreen University Hospital Trust (RLBUHT). (Study number 03/11/211/A).

Randomization

Patients were randomized using a computer-generated system which allocated them into two groups using blocked randomization. The block sizes were six for half of the blocks and eight for the other half, and the blocks were randomly permutated. The type of implant was selected immediately before surgery by opening an envelope with a previously randomized assignment. All envelopes used over the course of the study were opaque, well sealed and sequentially numbered to conceal the allocation assignment. Patients were unaware of the type of orbital implant inserted. Group I patients had a porous, hydroxyapatite orbital implant and Group II patients had a non-porous, acrylic orbital implant.

Surgical Technique

Enucleation and orbital implant insertion were performed both by senior surgeons and trainees. All procedures were performed under general anaesthesia. After induction of this anaesthesia, a retrobulbar injection of levobupivacaine 7.5mg/ml with 1:100,000 epinephrine was administered to prevent the oculo-cardiac reflex, reduce intra-operative haemorrhage and to avoid post-operative pain. A 360° conjunctival periotomy was performed. The conjunctiva and Tenon's capsule were released from the globe by blunt dissection performed in each quadrant. The four rectus muscles and the inferior oblique muscle were identified and secured with 6-0 glycolide/lactide sutures (PolysorbTM, CovidienTM, Mansfield, MA 02048, USA) before being disinserted from the globe. The superior oblique muscle was divided. The optic nerve was localized and briefly clamped with a blunt haemostat forceps before being transected using slightly curved scissors. The globe was removed and haemostasis was controlled by immediately inserting the orbital implant, exerting pressure for 3 minutes to expel any blood before it clotted. A 22-mm implant was used, except in individuals with small orbits, who had a 20-mm implant. An orbital implant sizer was used in some patients, when the choice was uncertain. A HA spherical orbital implant (OrbtexTM, Ceramisys Ltd, Sheffield, England, UK) or an AC implant (Wright Globe acrylic, John Weiss International, Milton Keynes, England, UK) was used. All implants were unwrapped and unpegged. The implants were placed in a solution of gentamicin 40mg/ml and levobupivacaine 7.5mg/ml for 5 minutes before insertion. The orbital implant was inserted intraconally. In the case of the HA implant, the inferior oblique muscle was sutured on an integrated absorbable suture platform (Figure 1a); the recti were sutured to each other and to the anchoring platform. Before insertion of the AC implant (Figure 1b), a 4.0 Ethilon (Ethicon. LLC, San Lorenzo, Puerto Rico, USA) was passed through a tunnel from the anterior to the posterior pole of the implant and along the temporal surface of the implant, before being tied with the knot at the posterior pole of the implant. (Possibly another figure) The inferior oblique muscle was sutured to this preplaced suture at the temporal equator of the implant and the recti were sutured to each other at the anterior pole of the implant. Tenon's capsule was closed with 4-0 glycolide/lactide (PolysorbTM,

CovidienTM, Mansfield, MA 02048, USA), and the conjunctiva was closed with interrupted 7-0 glycolide/lactide (PolysorbTM, CovidienTM, Mansfield, MA 02048, USA). Chloramphenicol ointment 1.0% w/w (Martindale Pharmaceuticals Ltd, Romford, Essex, UK) was administered and a plastic conformer shell (Optical conformer, Technovent Ltd, Bridgend, UK) was fitted before applying a pressure dressing. This consisted of three eye pads, two of which were folded, held in place by adhesive tape extending from the forehead to the cheek, and secured with a head bandage. Patients were kept in hospital for two days following the surgery for pain control and post-operative assessment. Patients were reviewed by an ophthalmologist four weeks post-operatively to assess the socket, and were subsequently seen by their ocularists after approximately 6 weeks for measurement and fitting of the prosthesis and then at six months for further assessment.

Outcome Measures

Our primary outcomes are patient-reported outcomes on lid position, ocular motility, surgical complication and satisfaction with treatment. Questionnaires designed for the study were sent to patients (summarized in online supplementary tables 1a). The patient's instrument consisted of 8 questions enquiring about the lid position, motility of implant, any complications associated with the implant and their satisfaction with the result. The questionnaires were mailed to patients at different time period at < 6 months, 6 to <18 months and/or ≥ 18 months following enucleation. All patients were asked to return the completed questionnaires in a prepaid envelope. With the patients' permission, a similar but simplified questionnaire was mailed to their ocularists, 6 weeks and 6 months following the enucleation (online supplementary table 1b, 1c). This had 8 questions (4 for the ocularist and another 4 for the patient) documenting ocularists' assessment on lid position, prosthetic motility, surgical complications and patients' feedback on adjustment to removal of eye, prosthetic motility and complications which are our secondary outcomes.

Statistical Analysis

A sample size of 141 eyes in each arm was required to provide a study power of 80%, with four primary outcomes and Bonferroni-corrected level of significance for each at 0.0125, to detect a difference in the rate of an adverse reaction of 5% in one group vs 20% in the other group for each outcome, and assuming 30% non-response rate. Intention-to-treat analysis was used: all patients received the allocated treatment at the time of randomisation and all patient's data were used regardless of loss from follow-up. For continuous variables we used a two-sample t-test to compare the means. For categorical variables we compared the distribution of the counts of responses across two treatments with the Chi-squared test or Fisher's exact test as appropriate. Kappa statistic was performed to measure inter-rater agreement.[19] We assessed potential selection bias caused by non response by comparison of the groups via demographic characteristics using t-test and test of equality of proportions. Significance was set at $P< 0.05$. For the four primary outcomes, a p value of <0.0125 was considered significant as we used Bonferroni correction to adjust for multiple comparisons (i.e. we reported unadjusted p-values and compared these with adjusted alpha=0.0125 to assure family-wise level of significance 0.05). For ocularists' outcomes we report the unadjusted p-values. All statistical analyses were performed with the statistical software Stata/IC V 13.1. (StataCorp LP, Texas, US).

RESULTS

Patient Demographics

The flow of randomization of subjects is detailed in Figure 2. Of the 281 patients included in the study, 139 patients were randomized to receive the hydroxyapatite implant and 142 to receive an acrylic implant. Patient demographics from mailed questionnaires and response rates are summarized in Table 1a. There were no significant differences in age, gender, follow-up time and response rate to

questionnaires between the two groups (P>0.05) giving no indication of selection bias due to non-response. The demographics of patients reviewed by the ocularists at 6 weeks and 6 months post-operative visits are shown in Table 1b. There were no significant differences between the two groups with respect to age and gender. There were significantly fewer responses from ocularists in the HA group at 6 months (P<0.001).

Patient-Reported Outcomes Measured by Mailed Questionnaires

Lid position, ocular motility and patient satisfaction

Patients-reported evaluations on lid position, prosthetic motility and satisfaction are shown in Table 2 (full version in online supplementary table 2). There are no significant differences between the groups as all P values are above the Bonferroni adjusted significant level of 0.0125. At ≥18 months, the upper lid position was considered the same as the fellow eye by 39.5% (34/86) patients with a HA implant and by 34.4% (32/93) with the AC implant (Fisher's exact test, P=0.647). The lower lid position was considered to be the same as the fellow eye by 54.7% (47/86) patients with HA and 58.2% (53/91) with AC (Fisher's exact test, P=0.660). Full eyelid opening was reported by 51.1% (45/88) patients with HA and 40.4% (38/94) patients with AC (Fisher's exact test, P=0.238). "Good" prosthesis motility was experienced by 37.9% (33/87) and 40.2% (35/87) patients with HA and AC implants respectively (Fisher's exact test, P=0.517). "Some" motility was reported by 55.2% (48/87) and 48.3% (42/87) patients with HA and AC implant respectively (Fisher's exact test, P=0.517). The overall prosthetic motility showed no significant differences between the groups (Fisher's exact test P>0.0125 in all, Bonferroni correction). Patient adjustment to removal of the eye was reported as "very good" in 58.2% (53/91) and 54.7% (52/95) patients with HA and AC implant respectively (Fisher's exact test, P=0.668). Responses that the prosthetic eye "looks like fellow eye" were given by 43% (37/86) patients with HA and 39.3% (35/89) patients with AC implant (Fisher's exact test, P=0.600).

Complications and further surgery

The complication rates and the need for additional surgery are summarized in Table 2 (full version in online supplementary table 2). There are no significant differences between the groups as all P values are above the Bonferroni adjusted significant level of 0.0125. At ≥18 months, complications reported by patients included socket discomfort (HA 51.6% [47/91]; AC 49.5% [47/95]), conjunctival discharge (HA 76.7% [66/86]; AC 82.1% [78/95]), suspected infection i.e. without positive microbial culture (HA 27.4% [20/73]; AC 26.9% [21/78]), inability to wear prosthesis (HA 2.7% [2/73]; AC 6.4% [5/78]), enophthalmos (HA 26.3% [20/76], AC 26.0% [20/77]) and superior sulcus deformity (HA 24.0% [18/75], AC 24.0% [18/75]). There were no significant differences between the groups in any complications reported (Fisher's exact test, P>0.0125 in all, Bonferroni correction). Extrusion of implant was reported by 1.4% (1/73) patients from HA group and 4.1% (3/74) patients from AC group (Fisher's exact test; P= 0.621). One of the three patients with AC implant extrusion required removal of the implant at 19.3 months because of tissue break down despite having a skin graft at 15.7 months. Correction of lid position at ≥18 months was required in 8% (7/87) patients receiving a HA implant at a median post-operative time of 26.5 months (range, 15.2-75.3) and in 5.3% (5/94) receiving an AC implant, at a median time of 12.8 months post enucleation (range 9.8-19.9 (the surgical date was unknown for two patients). Three of the 88 patients (3.4%) in the AC group required surgery to reposition the implant. There was no significant difference in the need for further surgery between the groups (Fisher's exact test, P>0.0125 in all, Bonferroni correction).

Patient-Reported Outcomes Elicited by Ocularists

When reviewed by the ocularists, 42.4% (42/83) patients with a HA implant reported having "good" prosthesis motility at 6 weeks as compared to 21.2% (14/66) patients with an AC implant (Fisher's

exact test, P=0.007). By 6 months, the results were comparable (HA 52.4% [33/63]; AC 50.0% [32/64](Fisher's exact test; P=0.830). There were no significant differences between the groups with respect to adjustment to removal of eye and to complications at 6 weeks and at 6 months (Fisher's exact test; P>0.05 in all). These results are summarized in Table 3a (full version in online supplementary table 3a.)

Ocularist-Reported Outcomes

Questionnaires completed by ocularists indicated no significant differences between the groups in lid opening, prosthetic motility and other complications at 6 weeks (Fisher's exact test, P>0.05 in all); at 6 months there was a higher prevalence of ptosis with AC than HA implants (46% vs 25%, Fisher's exact test P= 0.031) and a greater need for ocularists' treatment with HA than AC (50% vs 28%, Fisher's exact test P= 0.030) where topical antibiotics for conjunctival discharge or infection, polish or re-fitting of prosthesis were carried out. Table 3b summarizes the ocularists' assessments at 6 weeks and 6 months after enucleation (full version in online supplementary table 3b).

Direct comparison on prosthesis motility

Patients' responses on prosthesis motility at 6 weeks and 6 months were compared to those of the ocularists (Table 4a&b). The motility rating ("no", "some" or "good" movement) with the HA implant at 6 weeks showed a 77.9% agreement between patients and ocularists, which was a good agreement (Kappa=0.62) and significant (p<0.001). At 6 months there was a 77.8% agreement, which was moderate agreement (Kappa=0.59) and significant (p<0.001). With regards to the AC implant, the agreement on motility rating was 83.3% at 6 weeks, which was good (Kappa=0.61) and significant (p<0.001); at 6 months the agreement was 77.8%, which was moderate (Kappa=0.59) and significant (p<0.001).

DISCUSSION

Main Findings

The main finding of our study is that there were no major differences between hydroxyapatite and acrylic orbital implants with respect to patient-reported outcomes in lid position, ocular motility, complications and patient satisfaction after enucleation for uveal melanoma. There was a higher prevalence of ptosis in patients with AC implant and a greater need of ocularists' treatment in patients with HA implants at 6 months post-operatively observed by ocularists.

Strengths of Study

To our knowledge, this is the first randomized study comparing porous with non-porous orbital implants in patients who had enucleation as a primary treatment for uveal melanoma. We restricted our analysis to patients undergoing primary enucleation for uveal melanoma to evaluate the orbital implants without effects by scarring or deformity from previous injury or radiotherapy, which have complicated interpretation of the results in other studies. Another strength of our study is that outcomes were assessed both by patients and their ocularists, who provided objective validation of the patients' impressions regarding appearance and other outcomes. The randomization using well-sealed opaque envelopes was successful so that the two groups of patients were well matched in terms of demographics and follow up.

Limitations of Study

Some studies categorized prosthetic motility numerically using special recording device, although it may not be easily accessible in many clinical settings, such precision would have precluded

assessments by patients and ocularists, which we considered more meaningful and less likely to be subject to bias.[9] Secondly, complications such as 'infection' were largely interpreted by patients and ocularisits as increasing conjunctival discharge and redness +/- responded to topical antibiotics. Majority of cases did not have conjunctival swab or positive microbial culture as proof. Thirdly, not all questions were answered by patients and ocularists, so that true differences between implants may have been underestimated. Fourthly, some data from the early post-operative period are lacking because of the unexpected loss of a research assistant, which for several months prevented questionnaires from being prepared and mailed hence we have a slightly higher number of patients with over 18 months follow-up compared to that of less than 6 months. Lastly, patient-reported outcomes documented by their ocularists and ocularist-reported outcomes were not subjected to the correction for multiple comparisons, because they were secondary outcomes of our investigations. Some of the statistically significant associations may have occurred by chance, hence these results need to be interpreted with caution.

Comparison of outcomes between HA and AC implants

Problems were rare with both implants. Although there were some minor differences in outcomes during the early post-operative period, there were no significant differences between HA and AC implants after a median follow up of 27.8 and 32.8 months follow-up respectively.

Validation of Patients Reports by Ocularists

Patients and ocularists showed good agreement 6 weeks and 6 months after enucleation with respect to prosthetic motility. It was not possible to compare reported outcomes in regards to lid position and complications as these questions were phrased differently in the questionnaires (see online supplementary table 1b and 1c).

Previous Studies Comparing Porous with Non-Porous Implants

One relatively-small cohort study reported exposure of HA implants to be more common than that with silicone implants (11% of 27 patients vs 0% of 48 patients) after mean follow-up times of 10 months and 5 months respectively.[10] In contrast, Trichopoulos et al reported no difference between porous (HA/Medpor; 2.1% of 190 patients) and non-porous (polymethylacrylate [PMMA], 1.5% of 68 patients) implants after a median follow-up of 37.6 months.[7] A retrospective study reported no difference in motility without prosthesis between HA (31 patients) and alloplastic implants (45 patients) after mean follow-up times of 337 and 304 days respectively.[8] Colen et al reported no significant difference between acrylic and hydroxyapatite implants with respect to motility with prosthesis for any saccadic direction at a mean follow-up of 10.7 months.[9]

Comparison of Overall Outcomes with Previous Studies

Our results are comparable to those of Trichopoulos et al, Chao et al and Shields et al, in which most enucleations were performed for uveal melanoma.[7,15,17] Chao et al reported implant exposure (polyethylene) in 0.7% of 139 patients after a mean of 46.4 months and Shields et al reported exposure (HA) in 2% of 126 patients (3 children) over a mean follow-up of 14 months.[15, 17]

Despite different recording methods, our results with respect to motility with prosthesis at a follow-up of ≥6 months are similar to those of Custer et al and Colen et al as mentioned. [8-9] Chao et al observed ptosis in 2.9% of 139 patients with HA/polyethylene implants after a mean follow-up of 46.4 months.[15] In our study, 3.5% of 86 patients with a HA implant reported ptosis at ≥18 months (online supplementary table 2).

An important implication of our study is that despite the large differences in the cost of the implants, there are no significant long-term differences between HA and AC implants with respect to the outcomes reported by patients and ocularists. At the time of writing, each hydroxyapatite implants we used in the study cost £301.5 (approx. US$428.5) as compared to £15 (approx. US$21.3) for each acrylic implant. If we used acrylic implant in all our patients over the 7.5 years study period, this would have resulted in a total saving of £59,878.5 (approx. US$85,291.1).

The low complication rates and the high levels of satisfaction amongst patients and ocularists should be reassuring for future patients being counselled on likely outcomes of enucleation for uveal melanoma.

With regards to further studies, it would be useful to determine why ptosis, implant migration and other complications occurred in some patients and not others. There is scope for identifying risk factors for adverse outcomes as well as longer period of follow-up may require to detect complications such as extrusion which may not be apparent in the first 2-3 years post operatively. It would also be interesting to correlate patient-reported and objective outcomes with factors such as anxiety and depression, which may influence the patient's responses. We did not investigate the results of treatment for the various complications that occurred in our study. There would, for example, be scope for determining whether treatment for implant extrusion is more successful with one kind of implant than the other.

In conclusion, our study showed no major long-term differences between hydroxyapatite and acrylic implants with respect to patient-reported and ocularist-reported outcomes.

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LEGENDS

Figure 1. Flowchart showing patient inclusion from randomization and ≥18months follow-up. (A total of 41/43* and 35/37$^{\Delta}$ patients in the hydroxyapatite and acrylic groups respectively withdrew from the study because of overt metastatic disease.)

Table 1a. Demographic and Response Rate of Patients from Mail Questionnaire

Table 1b. Demographic and Response Rate of Patients from Ocularists' Responses

Table 2. Patient-Reported Outcomes Measured by Mailed Questionnaires on Lid position, Ocular Motility, Patient Satisfaction and Complication

Table 3a. Patient-Reported Outcomes Elicited by Ocularists on Adjustment to Enucleation, Ocular Motility and Complication of implant

Table 3b. Ocularists-Reported Outcomes on Patients' Lid Position, Ocular Motility, Complication and Need for Further Surgery

Table 4a. Agreement in Prosthesis Motility with Hydroxyapatite Implant Between Patients and Ocularists.

Table 4b. Agreement in Prosthesis Motility with Acrylic Implant Between Patients and Ocularists.