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CERAMIC ORBITAL IMPLANT: A STUDY OF THE EFFICACY, ACCEPTABILITY AND SAFETY OF A LOCALLY PRODUCED HYDROXYAPATITE ORBITAL IMPLANT FOR THE ANOPHTHALMIC SOCKET.

Dr Lewis Mark Levitz

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Ophthalmology.

Johannesburg, 2007

DECLARATION

I, Lewis Mark Levitz, hereby declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the branch of Ophthalmology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____

_____day of _____2007.

The work reported in this dissertation was carried out on behalf of the Wits Health Consortium and the data analysis forms one arm of a multicentre clinical trial.

The project was approved by the Ethics Committee, University of the Witwatersrand, and overseen by the Department of Arts, Culture, Science and Technology's Innovation Fund.

DEDICATION

To my wife Gillian and children, David and Jessica, for their interest and support.

To my parents, Abraham and Evelyn Levitz, for instilling in me a love for academia.

AWARDS, PATENTS AND PRESENTATIONS

Award

"The Helen Keller International Society of Ocular Trauma" poster award

VII International Symposium on Ocular Trauma
"New Synthetic Hydroxyapatite Orbital Implant"
Poster
Rome
Italy 2006
Presenter L Levitz

International Patents pending registration.

Orbital implant	PCT/IB02/04481	WO 03/037155 A2
Orbital implant applicator	PCT/IB2004/050408	WO 2004/0914531

Presentations

International:

"Eyeborn Orbital Implant"
South West Ophthalmic Meeting
Bristol
United Kingdom 2005
Presenter: L Levitz

Local:

"Hydroxyapatite Orbital Implants" Workshop
Ophthalmological Society of South Africa
Sun City
South Africa 2004
Presenter: L Levitz

ABSTRACT

A novel locally manufactured and developed porous hydroxyapatite orbital implant has been investigated and found to be as safe as commercially available implants.

Objective

To describe and analyze the results of twenty orbital implants implanted into patients in one arm of a multicentre trial.

Methods

A porous hydroxyapatite orbital implant with a smooth cap was developed and implanted into twenty patients. These patients were followed up for a period of four months. Patients were examined for signs of infection or extrusion of the implants. The amount of post-operative pain, chemosis, granuloma formation and vascularity was also assessed.

Results

None of the twenty patients had any signs of extrusion or infection at the termination of the study. There was very little pain or chemosis noted and no granuloma formation.

Conclusion

The locally developed implants were safe in anophthalmic eyes when reviewed after a four month follow-up period.

PREFACE

By 1997 there was an increasing interest in the design of porous orbital implants, which were getting more sophisticated. I helped to arrange the donation of ten such implants to a local state teaching hospital, and once implanted, spent several years following the patients up for complications. I also travelled overseas to meet experts in the field in the United Kingdom, Europe and Australia in an effort to understand the theory behind the new developments, which were fascinating to me.

In 1999 I was invited by Prof. T R Carmichael to join a Consortium being set up by the Bioceramic group of the Council for Scientific and Industrial Research (CSIR), Pretoria Eye Institute (PEI) and Wits Health Consortium (WHC), to develop a porous orbital implant that would be equivalent or superior to commercially available implants. I would be the sole representative of the Wits Health Consortium in this project. The Consortium would be funded by the Department of Arts, Culture, Science and Technology who would monitor the project.

The development of the implants was important to me as my patients were usually young indigent men who had been disfigured by the loss of an eye. I felt that if a good quality locally produced prosthesis could be made, I would be able to offer this to them at the State Hospital.

I have presented the results from this study in the United Kingdom and also in Rome where the poster won the Helen Keller award. There is interest in the new technology and the possibility that it will help patients well beyond our borders.

This study, with the resultant patents and development of novel technology, has led to the building of a factory to manufacture these orbital implants, most of which are now used in South Africa, and some of which are now exported.

ACKNOWLEDGEMENTS

1. Many thanks to Professor T R Carmichael for his continuous support in this project. His enthusiasm, professionalism and above all, sound practical advice have been an inspiration to me both in this research report and in my daily dealings with patients.
2. Many thanks to the members of the "Consortium" who helped to develop the orbital implant. They include Dr W du Preez, Dr W Richter, Dr M Thomas and Dr D Hope from the CSIR. The Pretoria Eye Institute was represented by Dr J Talma, Dr P Gous, Prof P Roux and Dr M Minnaar.

   Thank you also for giving me permission to use some of your data in this project.
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1.0 INTRODUCTION

This study is a data analysis of my findings in the Johannesburg arm of the "Bioceramic for Orbital Implants study" initiated by the Consortium. The results of this study will then be used to assess if the implants are safe, effective and biocompatible.

The aims of the Consortium study were to test the safety of a locally produced orbital implant that mimics the presence of an eye in a socket. The implant produced had to be safe and have a low rate of complications. If the prosthesis could meet these requirements, it could replace natural coral as the international standard base material for porous orbital implants, as it would be as safe and also be much cheaper than other porous implants.

The Consortium that developed the implant consisted of three organizations:

1. The National Product Developmental Centre, Bioceramic group of the Council of Scientific and Industrial Research (CSIR),

2. Meyer, König and Associates at the Pretoria Eye institute (PEI) and Pretoria Academic Hospital,

3. The Wits Health Consortium (WHC) of which I was the sole representative.

My role in the study was to conduct one arm of this trial to assess the acceptability and safety of an orbital implant of which I was a co-designer. The PEI would conduct the other arm of the study and our results would later be compared and combined.

The study was not intended to compare the merits of porous implants with non-porous implants but rather to assess the safety of the locally produced porous implant.

1.1 Local need for an orbital implant

Orbital trauma with ruptured globes leads to the loss of sight in many patients who present to hospitals in Johannesburg. If an eye is severely damaged and is irreparable, it is removed to prevent the devastating development of a sympathetic uveitis in the remaining good eye which may result in bilateral blindness. If no implant is inserted post enucleation or evisceration, the patient could be left with a disfiguring empty socket. Eyes may also be removed in cases of intraocular malignancies. This can result in facial abnormalities in children who require the presence of a globe to stimulate normal orbital development.[(1)]

1.2 History of orbital implants

Various implants have previously been used to try to replace the volume of a removed eye. The first reference to a prosthetic eye is 1600 years old and mentions a gold prosthesis.[(2)] Other implants have been made of glass, silicone, ceramic and acrylic.

Orbital implants have also varied in shape and in the way they have tried to add motility to a prosthesis placed under the lids. These implants have been modified with magnets, pins or grooves in an attempt to give a good cosmetic result. Extrusion is still a common problem with all these implants.[3]

Along with the advancement in materials used there have been great changes in the methods used to remove the affected eye. The crude method of threading a piece of thread through the eye, pulling forward until the eye protruded and then cutting out the eye with a sharp knife has been replaced with the removal of an eye from its capsule of tenons fascia, combined with the disinsertion of the ocular muscles. This has allowed placement of an orbital implant deep into the posterior tenons space where it forms a substitute for the volume of the removed globe.

Hydroxyapatite and porous implants allow tissue ingrowth which may results in a reduced risk of implant extrusion.[4] These implants are made from either naturally occurring coral, with its Haversian-like system of interconnecting pores, or from manufactured hydroxyapatite, which is a synthetic coral-like ceramic, in which pore size can be pre-determined. The pore size in hydroxyapatite is approximately 500μm in diameter.[5] Porous polyethylene[6] has also been used as a substitute for the natural hydroxyapatite.[7] Porous implants are well tolerated and provide prosthetic motility with few problems.[8] The vascularization of the implant is encouraged by its porous structure[9] with possibly a decreased rate of implant migration, extrusion and secondary infection.

It is with these thoughts in mind that the consortium decided to invent a new porous implant with a smooth cap. It was thought that having a smooth anterior surface would decrease the surface friction on the anterior surface of the implant and reduce the chance of extrusion.

1.3 Literature review

The most important considerations when considering the relative merits of various implants would be the issues of extrusion, exposure, infection and the factors which may predispose to these complications. This would include deciding on a porous versus a non-porous implant.

The next issue would be the measurement of the integration of the implant into the orbit and the assessment of this integration with radiological testing.

Following this one would assess the motility of the implant and the satisfaction of the patient.

Extrusion

Christmas et al [(1)] reported no extrusion with 123 orbital implants placed in paediatric orbits after a minimum of six months follow-up. Because seven different types of implants were used in this study of paediatric patients one cannot comment on the most appropriate implant type. Shields et al[(5)] in a study of 250 consecutive cases of hydroxyapatite implantation post enucleation, reported no extrusions. The mean follow-

up period in that study was 23 months. Christmas et al[10] reported two cases of extrusion (0.60%) in their series of 342 orbital implants. This resulted from exposure of one porous implant 420 days post implantation and exposure of an acrylic implant by day 14.

Custer et al[11] reviewed the knowledge gained between 1985 and 2001 by retrieving all articles relating to orbital implants published in English between those two dates. They stated that implant material and structure may impact on the incidence of several complications, including implant migration, infection, exposure and extrusion.
The authors were unable to find any evidence consistently documenting any type of implant having an absolute advantage over any other with regards to extrusion.

Exposure

It is difficult to get a true reflection of the incidence of exposure related to orbital implants. This is because various researchers have used different types of implants with varying surgical techniques in their studies. Follow-up periods are also not standardised.

Shields et al[5] reported an exposure rate of 1.6% (four of the 250 cases) with regard to hydroxyapatite. This had been the seminal study in orbital implants to date and included 250 patients who had received hydroxyapatite implants which had been wrapped in donor sclera. Buettner et al[3] reported tissue breakdown in 21% (eight of 37 patients) who had hydroxyapatite implants, with a mean follow-up time of eight months. The exposure was more common after evisceration and occurred in four of their six eviscerated patients.

Four of the 32 patients who were enucleated, as opposed to eviscerated, suffered from implant exposure. Shields believes that in these cases the tissue breakdown was due to inadequate tissue closure.[5]

Christmas et al[10] reported four cases of exposure in 342 patients who received orbital implants and were followed-up for a mean of 97 weeks. Of the group with hydroxyapatite implants, 1.1% (three of the 275 patients) had exposure of the implant. In the group who had acrylic implants, 12.5% (one of the eight patients) had exposure of the implant. This paper also summarized and tabulated the complications associated with orbital implants in the international literature between 1969 -1997.

Lee et al[12] studied the exposure rate in patients who had had implants following enucleation for retinoblastomas. The mean follow-up period was 21.6 months (range 3.0 - 55.0 months).Thirty of the 110 implants (28%) showed signs of extrusion. They suggested that the implant type and covering affected the exposure rate ($p< 0.01$). Their finding showed that hydroxyapatite and unwrapped PMMA implants (polymethylmethacrylate) had lower exposure rates in the paediatric orbit whereas Medpor (porous polyethylene) and mersilene-wrapped PMMA implants had a greater than 50% exposure rate. They gave the following exposure rates: Medpor 62% (8/13 implants), wrapped hydroxyapatite 11% (2/18 implants), and PMMA 8% (5/50 implants).[12]

In 2003 a review article by American Academy of Ophthalmologists[11] reviewed the previous major trials with regard to orbital implants. They mentioned that the study by

Nunery et al [13] found that there was a statistical difference (p=0.04) between the exposure rate of covered hydroxyapatite of 11% (n=7) and the zero rate of exposure in the covered silicone implants (n=48). However they noted that the silicone implants were only followed up for five months while the hydroxyapatite implants were followed up for an average of nine months. They contrasted this with the study by Christmas et al[10] who found that exposure developed in 1% of covered hydroxyapatite implants and none of the porous polyethylene implants. This was supported by the study by Dutton[7] who found no exposure in his series on covered hydroxyapatite implants. The study by Buettner et al[3] however reported an extrusion rate of 21% (eight extrusions in 37 patients) which seemed to back the report by Nunery et al.[13] The report by Remulla et al[14] showed exposure rates of 9% with porous implants. These three studies all had exposure rates of 9-21%. This was contrasted with the results by Karesh et al[6] who had no exposures in their study of porous implants. This would fit into the low reported incidence of exposure of porous implants suggested by Christmas et al[10]and Dutton.[7]

The summarising statement of this major review article was that the exposure rate of porous implants is similar to, or higher than that, of non-porous implants.[11]

Timing of exposure

Lee et al reported that 87% (26 of 30) patients had their exposure occur within one year.[12]

This contrasts with the study by Goldberg et al[15] who, in their study of the complications of hydroxyapatite implants in six patients, reported that exposure occurred four to six weeks (mean 4.5 weeks) after implantation.

Infection

Shields et al[5] reported one case of presumed orbital infection in 250 cases of hydroxyapatite implant. Christmas et al[10] reported one case of infection in 342 patients. One infected orbital implant was removed in the series of six cases of complicated hydroxyapatite implants reported by Goldberg et al.[15] Rubin et al[16] also believes that the increased prosthetic movement caused by a pegged implant may lead to conjunctival inflammation.

Migration

Christmas et al[10] reported no orbital migration in their study of 342 patients who had received orbital implants and had been followed up for a mean of 97 weeks.
Migration of an implant occurred in four of nine acrylic implants (44%) which had been implanted without integrating the rectus muscles and in one of the 108 hydroxyapatite implants (0.9%) in the paediatric study by Christmas et al.[1]



Figure 1.1: Previously used acrylic and silicone orbital implants with the new smooth capped implant (centre).

Porous versus non-porous implants.

Both porous and non-porous implants have the advantage of replacing the volume lost when a globe is removed. Both types of implant are inserted in the same anatomical position in the orbit. Both types of orbital implants can extrude and it is the desire to reduce the incidence of extrusion which has driven the investigation of alternative compounds which may be more biocompatible with orbital tissue.

Porous implants have been used in orthopaedic and craniofacial surgery.[4] They have the benefit of vascular ingrowth which prevents extrusion of the implant. The implants are non-toxic, non-allergenic and become integrated into the host by fibrovascular ingrowth.[10]

In the orbit, the vascular ingrowth may anchor the implant in the deep tissue and prevent extrusion. Porous implants are theoretically also less likely to become infected as they are incorporated with host blood vessels and have access to host immune defences.[8]

There is still some controversy about the use of porous implants. The use of non-porous implants is supported by previous findings showing that silicone implants had a much lower incidence of exposure when followed-up for three years.[13] The silicone or acrylic implants are cheaper and appear to have as good motility as unpegged hydroxyapatite.[17] The insightful editorial by Goldberg[18] gave a well balanced appraisal of the use of hydroxyapatite. On the one hand he described it as an "excellent porous implant", while warning that although it is "biocompatible, it is nonetheless a permanent foreign body". The fact that it is porous would actually increase the surface area of the implant exposed to the body and result in a greater inflammatory reaction. He also mentions that hydroxyapatite may not be the best implant for the occasional orbital surgeon.

The article by Viswanathan et al[17] shows that 56% of ophthalmologists questioned in the United Kingdom choose porous implants while 44% of the ophthalmologists questioned preferred using acrylic implants. The article states that "the majority of UK surgeons use porous spherical implants, similar to their US counterparts….porous implants have many advantages such as lighter weight, better prosthetic retention and cosmesis and possible pegging".[17]

The most comprehensive review on this subject by Custer et al[11] suggests that the exposure rate for porous implants is similar to or higher than that of non-porous implants and that patient selection and surgical techniques may impact on the exposure rates of porous implants.

Size of implants

Shields et al[5] suggests using a 16mm sphere in children less than six month, an18mm diameter implant in children aged six months to three years, and a size 20mm implant after the age of three. Buetter et al[3] states that the most commonly used sizes in his study were size 18mm and 20mm. De Potter et al[19] uses a size 20mm implant for adults and an 18mm implant for children. The most recent review of orbital implant trends in the UK[17] showed that 70% of respondents used size 18 to 20mm implants, with 6% using a size 16mm implant.

Pore size

Hydroxyapatite has a pore size of approximately 500µm. This structure eventually transforms into woven and then lamellar bone over time.[5] Synthetic implants pore size may vary between 900-1100µm in diameter.[20]

Motility

The previously published methods of measuring ocular motility have varied greatly. Some have not included measurements, [10, 16] while others measured the movement of a drop of ink painted on the conjunctiva and reported it in millimetres.[21] A method has been described where ocular saccades are measured using an electrode situated on the scleral shell. The patient is then placed in a magnetic search coil and the horizontal and vertical saccades are measured.[22] The difference in these methods includes the difference of a reference point; that being the centre of the scleral shell or the conjunctiva, the placement of a scleral shell at all, the availability of expensive radiological equipment and the difference in units reported, being reported in either millimetres or saccadic gain (saccadic amplitude divided by target amplitude). Movement of the prosthesis also depends on the size, shape and weight of the prosthesis.[21]

Recently an article by Raizada et al[23] has described a novel method of measuring implant and prosthetic mobility objectively. They use a custom–made slit-lamp with two rulers attached to each other, mounted on the slit-lamp's Hruby lens holder. The horizontal ruler is 15 cm long and the vertical ruler 5 cm long. The patient first has the centre of the socket with their implant marked with a pen, and then the patient's horizontal and vertical amplitudes are measured using photographs from a digital camera secured to the slit-lamp. The second stage would involve placing the prosthesis in the socket and marking the centre of the pupil. The range of ductions is then measured. This

relatively cheap modification of a slit-lamp may help in ensuring reproducible orbital implant and prosthetic motility measurements.

A practical reference range for "normal" motility of an orbital implant has also to be defined. Colen et al [22] provides a table with saccadic gain measurements for normal eyes compared with a reference search coil placed on a scleral shell. Although this was essential to prove that the movement of non-porous versus porous implants are equal, it is not practical for the average ocularist or ophthalmologist. Custer et al [21] provides a table with the movement of the socket after enucleation with an implant. This was measured with a mark placed on the conjunctival surface after the scleral shell had been removed. This can not be extrapolated to the movement of a scleral shell in the socket as the movement of the shell is limited by the fornices. It does however act as a guideline for expected ocular motility. Custer et al also excluded cases where less than six muscles had been reattached to the implant which was not done in the standard orbital implant technique described by Dutton.[7]

Expectations of what would be "normal" movement in an orbit with an implant are also varied. The argument put forward that the maximum amplitude of movement of an artificial eye is horizontal [21] was not substantiated in later tests which showed that the vertical "gain" was twice that of the horizontal "gain".[22] The argument that a prosthesis would be limited in abduction and adduction by the relative lack of movement of the fornices as compare with the greater movement of the fornices in upgaze and downgaze may indeed be valid.[22]

Vascularization

Porous implants allow fibrovascular ingrowth which anchors the implant in the orbit. The method of assessing this fibrovascular ingrowth has developed from technetium isotope scanning to magnetic resonance imaging (MRI). Currently contrast-enhanced MRI with surface coil appears to be the best imaging method for evaluating the hydroxyapatite orbital implant and its fibrovascular ingrowth.[19] The implant may be drilled and pegged, if required, after adequate vascularization of the implant has ocurred.[20]Imaging is done to assess the vascularization of the implant prior to drilling a peg into it.

De Potter et al[19]scanned 15 hydroxyapatite implants .Their finding was that there was no definite correlation between the extent of hydroxyapatite implant enhancement and the time interval after implantation. They attributed this to the various rates of angiogenesis in their patients. However, only three of the 15 patients showed diffuse homogenous enhancement with 11 being non-homogenous and one having only the anterior segment showing homogenous enhancement.

Eight years later a study on the fibrovascular ingrowth of porous polyethylene (Medpor)was published. De Potter et al[9] found that none of the ten patients in their study showed complete diffuse enhancement after 12 months. This was not, however, associated with an increased incidence of complications.

Sarvananthan et al[20] reported on their findings of eight synthetic porous implants scanned at least nine months after surgery. They found that five patients had moderate to large areas of non-enhancement of their implants more than nine months after the implant had been inserted. They concluded that this may be due to poor interconnectivity of the pores.

The timing of imaging is also controversial but a minimum of 6 months has been recommended.[24]

1.4 Local innovation

The CSIR and the Bone Research Unit of the Medical Research Council based at the Medical School of the University of the Witwatersrand have been developing and testing various ceramic and bone substitutes for medical use.[25] Porous hydroxyapatite had been fabricated at a local institution and animal studies on primates had been conducted.[25]

It was decided by the Consortium to use this expertise to develop a locally manufactured high quality hydroxyapatite orbital implant. The aim was to develop a light, inert and biochemically stable implant.[15] Hydroxyapatite was approved by the Food and Drug Administration in 1989[18] and had been used internationally for over ten years. The goal of our Consortium was to produce these implants cost effectively and to show their safe use in patients.

The implants were designed by the Consortium partners including myself and manufactured by the CSIR. The two main innovations would be the predetermination of pore size and the development of a smooth anterior surface of the implant.
Contact of the prosthesis with the conjunctiva may contribute to tissue breakdown.[3] The smooth anterior surface would be in contact with the patient's tissue and would be much less abrasive than commercially available coral or porous polyethylene. It was hoped that these innovations would decrease the chances of extrusion of the implant.

The implants were made by milling hydroxyapatite powder to submicron particle size and mixing it with an organic binder so that it could be pressed. Stearic acid spheres of size 700-1000μm were mixed in with the hydroxyapatite. The resultant mixture was pressed into dies to form a sphere with a smooth cap. This was then sintered at 1020 degrees Celsius for an hour. The stearic acid spheres melted leaving the predetermined interconnecting micropores. The implants were then cleaned, packaged and sterilized.



Figure 1.2: Orbital implant with a smooth cap

2.0 MATERIALS AND METHODS

2.1 Study design

This study was an analysis of the results of one arm of the multicentre Consortium study conducted by myself on behalf of the Consortium.

My arm of the study comprised 20 patients requiring enucleation or evisceration recruited between 1 September 2001 and 1 August 2002. This study would then be combined with a similar study performed by members of the Pretoria Eye Institute who along with the CSIR would comprise our research Consortium.

The study was coordinated by the CSIR and overseen by the Department of Arts, Culture, Science and Technology's Innovation fund (DACTS project 32532). I analyzed the results of my patients in the Johannesburg arm of that study, to assess the safety and acceptability of the orbital implant (OI). The study had been monitored by the DACTS innovation fund and the CSIR project manager.

Patients who required an eye to be removed were counselled as to the potential benefits and risks of an orbital implant. The operation was carefully explained to them and informed consent obtained. The patients were assured that they would have equal access to hospital care whether or not they chose to participate in the study.

2.1.1 Inclusion criteria

- Eviscerations/Enucleations required for ocular trauma in patients with a visual acuity of "no light perception" at presentation
- Eviscerations/Enucleations required for a painful blind eye
- Eviscerations/Enucleations requested by patient for cosmesis owing to an unsightly (phthisical) blind eye
- Patients without orbital implants requesting reconstruction

2.1.2 Exclusion criteria

- Patients with active orbital infection
- Pregnant or nursing women
- Patients with collagen-vascular diseases
- Patients on immunosuppressive therapy
- Patients that would not be available for follow-up visits
- Patients with intraocular tumours

The surgery was performed using internationally recognized techniques.[7] The patient would undergo a general anaesthetic. The conjunctiva would be reflected from the limbus with the anterior tenons capsule so that the extraocular muscles could be exposed. The horizontal and vertical rectus muscles were then tagged and all muscles detached from

the globe. The globe was then removed by cutting the optic nerve with either a wire snare or scissors. The globe was retracted from the orbit.

The implant was soaked in gentamicin and placed within the deep posterior tenons capsule with the smooth anterior face facing outward. The severed horizontal and vertical rectus muscles were sutured in a cruciate manner in front of the implant. The tenons capsule was then closed using size 6 0 absorbable sutures. The conjunctiva was closed with a similar absorbable suture. The absorbable suture was also brought forward from its attachment to a rectus muscle on the implant, to the corresponding upper or lower conjunctival fornix. A similar suture would tether the medial and lateral rectus to the medial and lateral aspects of the conjunctiva. These sutures would transmit the vector forces of the rectus muscles to the fornix and it would be the movement of the fornix which would impart movement to a scleral prosthesis.

All the surgery was performed by myself with an experienced assistant.

2.2 Size of implant

The CSIR provided Gamma irradiated orbital implants of three sizes, with diameters of 18, 20 and 22mm. The surgeon was allowed to choose the most appropriate size depending on the volume of the orbit. All packaging was sterile and batch numbers prominently marked.

2.3 Post operative management

A standardized post-operative regimen consisting of an intravenous dose of a broad spectrum antibiotic, cefazolin was used, with the surgeon allowed to switch to another antibiotic with a similar spectrum of anti-microbial activity if the protocol antibiotic was not available.

The patients were seen on day one after the operation and then weekly for two weeks. They were examined monthly until the four month follow-up period was reached. The patients were followed up for evidence of pain, chemosis, exposure, migration, extrusion, infection and granuloma formation.

2.4 Outcomes measured

All examinations were done by myself after which the patients were sent on to an ocularist for further examination using the same criteria. The ocularist would also make the scleral prosthesis. The period of follow up was four months.

1. Pain

Pain was graded as being present or absent at all visits. Patients were given analgesia as required post operatively according to the protocol.

2. Chemosis

Chemosis was noted and the management of the condition documented.

3. Exposure

Exposure was documented if the white implant could be seen through a dehiscence of the wound. Exposure of the implant was divided into either small (1-5mm), medium (6-9) or large (10 mm or greater).

4. Migration

Migration was documented and the position of the migration noted.

5. Extrusion

Extrusion was noted as being present or absent.

6. Infection

Infection was noted as being present or absent.

7. Granuloma formation

Granulomas, which may result as a complication of surgery, were noted and would be defined as infected or sterile.

8. Motility

Ocular motility was measured with the patient sitting facing the examiner and with the prosthesis in the conjunctival fornix. The patient was asked to look left, right, up and down. The maximum ductions were measured in millimetres from the initial primary position. An estimate of the degrees of movement could be calculated by multiplying the

number in millimetres by a factor of seven to get a result in degrees of arc. This would indicate to what extent the implant allowed the prosthesis to move like a normal eye. The total number of millimetres of movement in abduction, adduction, elevation and depression were added together to measure total movement of the eye. The mean ocular movement in four positions of gaze of the 19 patients could also then be calculated.

9. Vascularization

The vascularization of the implants had to be assessed. Two of my patients had magnetic resonance imaging (MRI) scans at six months to assess the level of vascularization. It is thought that the greater the vascular ingrowth into the implant, the less chance it has of migrating out of the socket.[8]

10. Acceptability

The patient's satisfaction with the implant and their cosmesis was recorded. There was a five point scale and the patient could indicate if they thought their appearance was unacceptable, poor, acceptable, good or excellent.

I would use the same scale to document my satisfaction with the cosmetic result at the four month visit after the operation.

2.5 End points

The end points were set by the CSIR and reflect their research into what would be considered to be equal or better than currently manufactured implants:

Ha: The implant is as effective as commercially available implants.

Ho: The implant is not as effective as commercially available implants.

The implant would be considered effective if it showed the following:

- Extrusion of 0%
- Exposure of less than 10%
- Migration rate of 0%
- Conjunctival lesion (pyogenic granuloma) of less than 1%
- Implant infection rate of less than 1%

2.6 Data analysis

All the information was recorded on a standard form and then placed onto an Access and Excel worksheet. The Biostatistical Unit of the Medical Research Council advised on the use of an appropriate statistical model.

A successful implant was defined as having no extrusion. A Simon Two-Stage design was chosen. This allowed an initial group of 20 patients to have the implant operation and the results analyzed. If the study showed the implant to be safe, a further 20 operations would be done. The results would then be re-analyzed using the same criteria.

For ethical reasons we chose strict criteria which considered 0.9 a poor success rate and 0.99 a good rate, with α=0.05 and β=0.02. The confidence limits would therefore extend no further than 0.057 in either direction of the observed success rate. If after the initial 19 patients, there were 17 or fewer successes the study would be terminated. If the study showed the implants to be safe a further 20 operations would be performed. Using the above mentioned criteria, the success rate would be acceptable if 38 of the 40 implants were successful.

With such strict criteria, the expected probability of an early ending of this study was 0.8.

2.7 Imaging

As an aid to understanding the vascularization of the implant, I performed MRI scans on two of the patients. The process and method of scanning has been well described.[9,19,20,24]

3.0 RESULTS

3.1 Demographics

3.1.1 Age and sex

There were 17 male patients and three female patients. The age ranged between 21 and 27 years (mean age 25 years) for the female patients, and 21 and 52 years for the male patients (mean age 33 years) . (See Table 3.1)

Forty two percent of the patients (8 of 19 patients) who had lost an eye due to trauma were less than 30 years.

3.1.2 Diagnosis

Twelve patients requested that they have surgery to improve their cosmesis. They either had an empty socket from previous surgery, phthisis or an unsightly scar. A further two patients had their eye removed at the time of trauma. The remaining six patients asked that the blind eye be removed as it was painful. (See table 3.1)

3.1.3 Predisposing factors to the loss of an eye

Nineteen of the twenty patients lost their eye due to trauma. Twelve of these injuries were due to non-accidental trauma. This included seven eyes which were lost due to stab injuries, three eyes lost due to gunshot injuries and two patients who lost vision when

struck across the face with a whip. The only patient who did not suffer trauma lost his vision from a corneal scar and ulcer related to thyroid eye disease. (See Table 3.1)

Table 3.1 Demographics and follow-up periods of 20 patients who received orbital implants

Pt No	Age	Sex	Reason for enucleation	Predisposing factor	R/L	Primary/Secondary	Size	Months Follow up
1	27	F	Painful Blind Eye, Ruptured Globe	Trauma, stab	L	P	18	29
2	52	M	Painful Blind Eye	Thyroid, crisis	R	P	18	51
3	24	M	Painful Blind Eye, Ruptured Globe	Trauma, stab	L	P	18	4
4	41	M	Painful Blind Eye	Trauma, stab	L	P	18	4
5	37	M	Painful Blind Eye	Trauma	L	P	18	4
6	24	M	Cosmesis	Trauma, accident	L	S	18	4
7	29	M	Painful Blind Eye	Trauma, hit with stone	L	S	18	3
8	42	M	Cosmesis	Trauma, stab	L	S	18	6
9	20	M	Painful Blind Eye	Trauma, whip injury	R	S	18	5
10	45	M	Painful Blind Eye	Trauma, stab	L	P	18	5
11	27	F	Cosmesis	Trauma, accident	L	P	18	8
12	37	M	Cosmesis	Trauma, stab	L	S	20	9
13	21	M	Cosmesis	Trauma, fireworks	L	P	18	6
14	31	M	Cosmesis	Trauma, gunshot	R	S	18	4
15	32	M	Cosmesis	Trauma ,whip injury	R	S	18	16
16	21	F	Cosmesis	Trauma, gunshot	L	S	18	13
17	32	M	Cosmesis	Trauma, stab	L	S	18	4
18	42	M	Cosmesis	Trauma, stone	L	S	18	5
19	28	M	Cosmesis	Trauma ,MVA	R	S	18	28
20	30	M	Cosmesis	Trauma, gunshot	L	S	18	7

R = Right
L = Left
MVA = Motor Vehicle Accident
P = Primary implant
S = Secondary implant

3.2 Pain

Ten patients described having ocular pain on day one post surgery. This decreased to four patients on day two after the operation. By week one only one patient had ocular pain. No patients had any pain by week two.

3.3 Chemosis

Six patients had chemosis on day one post surgery. This decreased to five on day two and only one at week one post surgery. There was no chemosis noted in any patient by week two.

3.4 Exposure

No patients suffered from any form of exposure during the study period.

3.5 Migration or Extrusion

This was the most important aspect of the study as any extrusion may have resulted in the termination of this arm of the study. No patients suffered extrusion during the study period.

3.6 Infection

There were no cases of implant or orbital infection.

3.7 Granuloma

There was no granuloma formation in any of the patients.

3.8 Motility

Ocular motility was documented between weeks four and six with the patient sitting in front of the examiner with their fitted scleral shell. The extent of the ductions was measures with the patient abducting, adducting, elevating and depressing their artificial "eye". These measurements were then converted to degrees of arc by multiplying by a factor of seven. The measurements of 19 of the 20 patients were available for analysis. (See Table 3.2)

The mean value of the sum of abduction, adduction, elevation and depression in the 19 patients was 11.8mm (82º); the range was from 3mm to 19mm (21º-133º).

The mean value for abduction was 2.8 mm (19º), range 0mm-5mm (0º-35º). The mean value for adduction was 3.0 mm (21º), range from 0mm-5mm (0º-35º). The mean value for elevation was 3.0 mm (21º), range from 2mm-5mm (14º-35º), and the mean value for depression was 2.9mm (20º) range from 0mm-5mm (0º-35º).

Table 3.2. Measurement of ocular motility in millimetres

Patient number	Abduction	Adduction	Elevation	Depression	Total motility in millimeters
1	5	4	5	5	**19**
2	4	4	4	4	**16**
3	2	3	2	4	**11**
4	3	4	2	0	**9**
5	2	5	4	5	**16**
6					
7	1	1	2	3	**7**
8	2	2	3	2	**9**
9	3	3	4	3	**13**
10	3	3	4	3	**13**
11	4	4	4	4	**16**
12	3	3	3	3	**12**
13	3	3	3	3	**12**
14	3	3	3	3	**12**
15	3	3	3	3	**12**
16	4	3	3	3	**13**
17	3	3	2	2	**10**
18	3	3	2	3	**11**
19	0	0	3	0	**3**
20	3	3	2	3	**11**
Mean (range) of ocular ductions	**2.8 (0-5)**	**3.0 (0-5)**	**3.0 (2-5)**	**2.9 (0-5)**	**11.8mm (3-19)**

3.9 Vascularization

Two patients had Gadolinium enhanced MRI scans of their orbits at six months. Both showed incomplete patchy vascularization of the outer third of the implant.

3.10 Primary versus secondary implants

Eight patients had implants at the time of initial surgery. The remaining 12 patients had previously undergone eye surgery that included evisceration or enucleation. They presented to the hospital eye clinic in an attempt to improve their cosmesis as they had empty sockets.

3.11 Size of implants

Nineteen patients had an 18mm implant and one patient had a 20mm implant.

3.12 Follow-up period

Only one patient did not have a complete four month follow-up record. Compliance was encouraged by having a scleral shell made by an ocularist who would then follow the patient up at their clinic. The patients were told that their scleral shell would be replaced free of charge should it be damaged or become uncomfortable. If patients missed an appointment, they were contacted telephonically to see if there were any problems with their implants. No patient reported any such problems.

3.13 Acceptability

Seventeen patients regarded their result as being excellent. Two thought that their results were good and one thought the result acceptable. The surgeon thought that there were 16 excellent results, three good and one acceptable result. The only difference between the surgeon and the patients was confined to one patient who thought his result excellent, while the surgeon thought it good.



Figure 3.1: 3-D CAT scan showing the orbital implant in the orbit

4.0 DISCUSSION

The epidemiology of the patients in this study conforms to that reported in the United States where May et al[26] reported a male to female ratio of 5:1. In my study there was also a preponderance of male patients with the male to female ratio of 5:1 (16 male patients: 3 female patient) who had lost an eye due to trauma. There was a difference in the reported age of the patients with eye injuries due to trauma, with 42% being under the age of 30 years in this study, whereas May et al[26] reported that 58% of the first 8 952 patients registered in the United States Eye Injury Registry were less than 30 years old.

Pain was reported in eight of the 20 patients on the first day following surgery as can be expected after orbital surgery. This decreased to four patients on the second day. No patients had any pain by week two. Chronic pain starting on day 14 post implantation has previously been reported in a non-porous implant which later had to be exchanged.[10]

Transient chemosis was seen in six patients (30%) in the first few days as might be expected after orbital surgery. There was no chemosis noted by month one. This is a result of the implant being well tolerated in the orbit. Chemosis has been reported in the literature to be so marked that a temporary tarsorrhaphy had to be used for a week following implant insertion.[20]

There was also no tissue breakdown or extrusion in my patients. This compares favourably to the results reported by Christmas et al[10] who had only one case of exposure leading to extrusion in their series of 342 patients. This extrusion occurred in one of the 275 hydroxyapatite implants. Initial exposure was noticed two weeks after the implant had been inserted and was documented to be due to recurrent infection. The patient later went on to extrude a year after implantation.

Extrusion has been noted to appear between four to six weeks[15] post implantation but may take up to 30 months to manifest[14] with most extrusions occurring within six months of implantation. A previous study[14] has suggested an extrusion rate of 9%. In order to reduce this we used an implant with a smooth anterior surface which would be less likely to "cut its way out" of the orbit.

Although one of the 20 patients did not complete the four month follow-up period, I have followed the remaining 19 patients for up to 51 months (mean 11.3 months). My results therefore compare favourably with those reported by Dutton[7] who had no extrusions in their series of 50 patients receiving hydroxyapatite implants. Their series had a follow-up period of between two to 27 months with a mean follow-up period of 10.4 months. Shields et al[8] also reported no hydroxyapatite orbital implant exposure or extrusion in 100 cases followed up for a mean of 11 months. Shields et al[5] reported no extrusion in 250 hydroxyapatite implants with a mean follow-up of 23 months. They did, however, report four cases of conjunctival erosion but noted that three of those four cases were in children less than five years old.

My study did not find the large percentage of implant exposure noted by Nunery et al[13] who found that 11% (seven of their 59) hydroxyapatite implants extruded. Their follow-up time was nine months for hydroxyapatite implants. Lee et al[12] also reported an exposure rate of 11% (two of 18) hydroxyapatite implants in their study on eyes enucleated for retinoblastoma. They did, however, qualify this with the statement that both hydroxyapatite and plain PMMA implants appear to have lower exposure rates in the orbit than Medpor and mersilene-wrapped PMMA where more than 50% developed exposure of the implant.

The results from my study, with its four month follow-up period, also differs from the results by Buettner et al[3] who found a 21% exposure rate of hydroxyapatite implants. In their study the exposure was noted between two to 16 weeks post surgery (mean 6.2 weeks). Although it is possible that some exposure may occur after the four month follow-up period, neither I nor the ocularist have been made aware of any problems. I have followed five patients for up to three years or more and have had no extrusion, granulomas, migration or exposure. As the patients would receive new scleral shells free of charge for life, as was the arrangement with the participating ocularists, there would be no financial deterrent for them to present to the ocularist if they had any discomfort or problem with the implant.

There is no universal method of measuring ocular motility after enucleation. My method is easier and cheaper than the very elegant and sophisticated use of magnetic search coils used by Colen at al.[22] Here the ocular movement was measured in saccadic 'gain' (saccadic amplitude divided by target amplitude) and were used to show that the motility

of unpegged hydroxyapatite and acrylic implants are similar. The measurements listed in that paper, although accurate, would not be reproducible in the average ophthalmologist's practice.

The closest measurements that can be compared to those found in my study are those reported by Custer et al.[21] The limitations of this comparison are that Custer sutured six rectus muscles to the orbital implants, as compared with the four rectus muscles sutured in my study, in keeping with the protocol described by Dutton.[7] Custer et al[21] also measured the movement of a mark placed on the conjunctiva compared to the centre of the fitted scleral shell.

With these limitations in mind, my study found a mean horizontal movement of 5.8 mm and a mean vertical movement of 5.9mm. Custer et al[21] found a mean horizontal movement of 9.1mm and mean vertical movement of 7.3mm. The lower ranges found in my study might be due to the limiting effect of the fornix on the implant described by Colen et al.[24] I did not find that the horizontal movement greater than the vertical movement as reported by Custer et al[21] or the opposite as reported by Colen et al.[22] The use of a modified slit-lamp recently suggested by Raizada et al[23] will go a long way in standardising measurements, as the adaptations to the slit-lamp are easy to make and no special equipment is needed, with the exception of a digital camera. The measurements made in my study were also made in millimetres and will therefore be comparable with measurements taken using the modified slit-lamp method.

The MRI scans of two patients done at six months show patchy vascularization of the outer third of the implant. There was no capsule seen around the implant as may be expected with a silicone or acrylic implant. The low rate of visualized vascularization may be due to the fact that it may take six to ten months to vascularize, but even this cannot be uniformly predicted. Patchy vascularization may also be due to poor interconnecting pores within the implant.[20]

This finding is in keeping with previously reported accounts of poor vascularization occurring in synthetic porous implants even when scanned nine months after implantation.[20] My study also confirms the findings of De Potter et al[19] who found non-homogenous enhancement in ten of the 15 hydroxyapatite implants scanned. Eight years later it was shown that none of ten porous polyethylene (Medpor) implants showed complete homogenous enhancement when scanned at one year.[9]There is rarely full homogenous enhancement of porous implants, regardless of the material they are made from, be it a synthetic material,[20] hydroxyapatite,[19] or porous polyethylene.[9]

Prior ocular surgery may also delay fibrovascular ingrowth.[9] Scans may also not reflect the level of implant vascularization accurately. Thus the amount of vascularization seen on MRI scans of porous implants may be universally disappointing and less than expected. The method of demonstrating complete vascularization also influences interpretation. Previous 99m technetium-MDP static bone scans which were used in early studies of vascularization do not provide the same amount of anatomic detail as in Gadolinium enhanced MRI scans. Even with the MRI scan being performed there is no

standardized method of reporting in terms of segment vascularized or concentric sections vascularised.

Nineteen patients had a size 18mm implant and one had a size 20mm implant. This is in keeping with the study by Buettner et al[3] who used mainly size 18mm and 20mm porous implants and mirrors the current trend in the United Kingdom where 70% of respondents chose to use a size 18-20mm implant.[17]

The implant was chosen by assessing the amount of volume to be replaced in the orbit, and also taking into account the fact that some orbital volume would be taken up by the prosthesis. This may be consistent with the findings of Christmas et al[1] who used a mean size of 18mm implant, however their patients were exclusively children. Shields et al[5] however suggest a size 18mm implant in children and a 20mm sphere in adults.

Seventeen patients (85%) regarded their result as being excellent. Two (10%) thought that their results were good and one (5%) thought the result acceptable. This correlated well with the surgeon who thought that there were 16 (80%) excellent results, three (15%) good results and one (5%) acceptable result. The only discrepancy between the surgeon and patient involved patient number ten. Although the patient thought the result excellent, the surgeon thought that the upper sulcus looked a little shallow. This would indicate that the surgeon had higher expectations of the surgery than were held by the patient. This correlates well with the study of 123 implants by Christmas et al[1] who found that the surgeon thought the cosmetic appearance was good in 96% (118 of the 123

patients).Their observations were based on subjective observer grading and may be biased.

In order for the implant to meet the criteria of currently available implants, it had to meet the following criteria:

- Extrusion of 0%
- Exposure of less than 10%
- Migration rate of 0%
- Conjunctival lesion (pyogenic granuloma) of less than 1%
- Implant infection rate of less than 1%

All these criteria were met in this arm of the study. There were no cases of migration, extrusion or infection. The implant resulted in no conjunctival erosion, conjunctival lesions or granulomas.
The study therefore met all the required end points at four months follow-up.

The results of the currently reported arm will be added to the arm with 40 patients at the other participating centre, and the results analyzed to see if the final trial end points are reached with 60 participating patients.

The CSIR and the Bone Research Unit, Medical Research Council, University of the Witwatersrand have many years of experience with hydroxyapatite use for medical purposes. [25] This research has been used for medical and dental applications. The

marrying of this local expertise with the clinical need for the development of an affordable high quality implant has resulted in our locally produced implant being produced at a cheaper price. This has resulted in these implants being available to the South African public at a price half of that of other porous implants.

5.0 CONCLUSION

The results of this arm of the two-centre study into the safety of a locally produced implant show that the locally produced hydroxyapatite implant is safe in anophthalmic eyes with no incidence of inflammation, infection or extrusion when followed for a period of four months.

6.0 RECOMMENATIONS FOR FUTURE WORK

It became obvious when designing this study that there were large areas not yet fully explored with regard to the study of orbital implants. There therefore exists an opportunity to "make a mark" upon this field and explore these areas as opportunities for future research. These areas would include the following:

1. There is no universally agreed upon method for measuring the motility of an artificial eye. Although this is of importance to the patient, there is no agreed upon method in the literature. One cannot therefore compare movement between the studies [16,22,23] and decide whether the saccades and range of movement are comparable. The development of a standard method of measuring the saccades and range of movements of either the fornix or the implant would be a major

advance in the study of the anophthalmic socket. The adaption of the slit-lamp as suggested by Kuldeep et al[23] has gone some way in addressing this problem.

2. There is no agreed upon grading with regard to the vascularization of porous implants. A system taking into account the volume of the implant and dividing the volume into measurable concentric segments of similar volumes which can be quantified would make the comparison of vascularization of implants possible. An attempt to use manual contouring and calculating the percentage area of enhancement has been reported but it has not been repeated in further studies.[9] A standardised reproducible grading system would then make it possible to determine which implants are really fully vascularized. A system describing a standardized Gadolinium intensity would also standardize results from studies and lead to more comparable reporting.

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