NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of insertion of a hydrogel synthetic keratoplasty

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2003.

Procedure name

Synthetic penetrating keratoplasty using a synthetic hydrogel cornea.

Specialty society

Royal College of Ophthalmology.

Description

Indications

The cornea is the transparent part of the coat of the eyeball that covers the iris and pupil and admits light to the interior of the eye.

Injury or disease can cause the cornea to become opaque, hindering the passage of light and resulting in vision loss. Diseases that can cause the cornea to deteriorate include keratoconus, bullous keratopathy and herpetic eye disease.

Current treatments and alternatives

A corneal transplant involves the removal of a disc of tissue from the centre of the eye using a trephine and replacing it with a corresponding disc from a donor eye. In penetrating keratoplasty, the disc removed is the entire thickness of the cornea and so is the replacement disc. The donor cornea is attached with extremely fine sutures.

Some patients cannot undergo standard penetrating keratoplasty with use of donor tissue for several reasons such as disease severity, objection to the use of donor tissue, failed past donor tissue transplants, or where measures required to prevent

graft rejection are medically contraindicated. For these patients, penetrating keratoplasty using an artificial cornea or keratoprosthesis is an option.

The clinical need for an alternative to donor tissue has sparked considerable research interest in the development of new keratoprostheses. One technique that has been developed as a result of this is synthetic penetrating keratoplasty using a synthetic hydrogel cornea.

What the procedure involves

The implantation of synthetic hydrogel cornea is a two-stage surgical procedure. The first stage involves an incision made through the sclera and into the cornea to create an intralamellar pocket. A portion of the central part of the posterior lamella is removed using a trephine, and the synthetic hydrogel cornea is inserted into the intralamellar pocket. The incision is then stitched closed with sutures.

In most cases, the operation is completed by the formation of a flap of tissue from the conjunctiva (the outer layer of the 'white' of the eye), which is used to cover the surface of the front of the eye. This may cause changes in the cosmetic appearance of the eye.

Twelve weeks post-implant the second stage of the procedure is performed, where the conjunctival flap and a thin layer of the cornea are removed, exposing the synthetic hydrogel cornea to light. The eye may still not appear completely 'normal' after this stage of the operation.

The procedure is reversible; if problems occur following the procedure the implant can be removed and replaced, either with another implant or with a donor corneal graft, to restore to preoperative status.

Efficacy

Evidence on the efficacy of this procedure is based on small, uncontrolled studies with short-term follow up. Initial results indicated that most patients maintained or experienced improved visual acuity (though still poor) following the procedure. In a report of 41 patients with a mean preoperative visual acuity of hand movements, mean best corrected visual acuity for 21 patients at12 months follow up was 20/300. The authors of this report also stated that of the 41 patients undergoing implant of a synthetic cornea, 26 implants remained in situ (63.4%) with a mean follow up of 16 months. Patient selection criteria have changed however since the first trial on this procedure, and it is unclear what impact this will have on efficacy outcomes.

The Specialist Advisors considered that this procedure should be restricted to those individuals who cannot be treated with already established procedures. One Advisor stated that while post-operative vision is not very good for most cases it is better than the pre-operative situation.

Safety

Stromal melting is a common complication for all keratoprostheses and is common following this procedure. In a review of 41 nonherptic patients who had undergone synthetic penetrating keratoplasty using a synthetic hydrogel cornea 41.5% of patients developed a stromal melt. Although the number of patients requiring device removal as a result of this complication was unclear in this review, in a series by the same authors it was reported that 12.5% (5/40) implants were removed because of melting. Other complications included optic depositions (22%) development of retroprostheitc membranes (7.3%) and retinal detachment (4.9%). The literature also seems to suggest that there are certain patients who are at increased risk of complications, namely herptic patients and smokers.

There were no reports of endophthalmitis leading to the loss of an eye.

The Specialist Advisors considered that the long-term complication rate of this procedure is unknown. Endophthalmitis is the most significant potential complication of any artificial cornea but has not yet occurred following this procedure. Extrusion of the device usually due to the development of retroprosthetic membranes is another serious complication and occurs in around 5% of cases. One Advisor commented that opacification of the device is an inherent problem due to the hydrogel material and may limit the life of the procedure.

Literature reviews

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to synthetic penetrating keratoplasty using a synthetic hydrogel cornea. Searches were conducted using the following databases: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index, and covered the period from their commencement to August 2003. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good-quality comparative studies. Abstracts were excluded where no clinical outcomes were reported, or the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with a poor prognosis for penetrating keraptoplasty with donor tissue.
Intervention/test	Implantation of synethic hydrogel cornea.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on five studies. Four of these studies are described in the efficacy section of this document and all five studies are included in the assessment of safety.

Appendix A includes a list of relevant studies not included in the summary tables

Table 2 Key efficacy and safety outcomes

Study details	Key efficacy outcomes	Key safety outcomes	Comments
Hicks et al (2002) [1] and Hicks et al (2003) [2] Study design: case series Assessment of patients who had received implantation to the end of November 2001. 38 patients (40 implants) Patients were included if they were adults whose corneal pathology was unsuited to management by means of a conventional corneal graft. Peroperative visual acuities were perception of light (PL) to 6/60 (20/200). Mean: hand movements (HM). Mean age:60 years (range 20–83 years) Mean follow up: 10.1 months (range 2 weeks–36 months) As of 30 November 2001 • 26 patients had completed stage II surgery. • 12 patients had more than 12 months follow up • 24 patients had more than 6 months follow up.	At follow-up (November 2001) **Visual acuity** **Preop** Minimum Perception light (PL) Mean HM-CF Maximum 20/200 **Best unaided visual acuity** Minimum Perception light (PL) Mean CF-20/200 Maximum 20/80 **Best corrected visual acuity** Minimum Perception light (PL) Mean 20/120-20/80 Maximum 20/30 – 20/20 33 patients/cases (82.5%) had retained device, removed and replaced with donor tissue in five cases (12.5%)	**Device related** • 5% of cases diffuse brown optic deposition (due to medication and smoking) • 7.5% of cases diffuse white optic deposition • 2.5% of cases discrete branching • 5.0% of cases where device needed to be removed due to depositions • 30% of cases stromal melt • 6 of these patients had HSV – representing 75% of patients with HSV. • 5 device (12.5%) removals due to melting	Not clear whether consecutive patients. Change in protocol during the study: first patients were prescribed medication – this was subsequently discontinued (results are presented in separate paper [3]). Devices were supplied by manufacturer. Percentages calculated on number of implants rather than patients. Absolute figures not given for BCVA – figure presented. Text and figures difficult to reconcile with BCVA and complications. Authors again note that corneal melts were found to be associated with history of ocular herpes simplex infection (HSV). (8 with HSV 32 without HSV). Figures based on number of implants (40) rather than number of patients (38).

Study details	Key efficacy outcomes	Key safety outcomes	Comments
Crawford et al (2002) [4] 14 consecutive patients Study design: case series Inclusion criteria and exclusion criteria clearly stated. Preoperative visual acuity (VA): 13 patients had visual acuity in the range of HM-CF. One patient was only able to distinguish light. Mean number of failed grafts; two (range 1–4). Mean follow up: 13.3 months (range 1–29 months)	**Best-corrected visual acuity** Patients Pre Post Follow up 1 HM 20/60 (29 months) 2 HM HM (29 months) 3 HM CF (25 months) 4 HM CF (25 months) 5 HM CF (14 months) 6 HM 20/60 (13 months) 7 CF HM (13 months) 8 HM 20/30 (13 months) 9 CF 20/20 (8 months) 10 HM 20/400 (8 months) 11 CF N/A (4 months) 12 CF N/A (3 months) 13 HM N/A (1 month) 14 LP N/A (1 month) Postoperative visual acuity (VA): ranged from hand movements (HM)–20/20. One patient visual acuity has worsened since procedure (also had optic deposits) At follow-up 93% (13/14) had retained the device.	**Complications** • 2 patients (14%) optic deposits (brown – due to smoking) • 1 patient (7%) stromal melt	Termed a phase I human clinical trial. Initial results. Device has since changed name.
Hicks et al (2003) [5] 41 patients (nonherpetic) Data in the reports are current to the end of January 2003. Age at implantation raged from 20–83 years. All patients had between 0–4 failed	Nonherpetic cases (41) **Best-corrected visual acuity (BCVA)** Min Mean Max Preop PL HM CF 3 months PL CF 20/35 6 months PL 20/400 20/35 9 months NPL 20/400 20/60 12 months NPL 20/300 20/30	**Complications in nonherpetic cases** • 0 % patients endophthalmitis • 41.5% stromal corneal melt • 9.8% diffuse brown deposit within the optic • 9.8% diffuse white deposit within the optic • 2.4% fungal deposit • 7.3% optic surface spoliation • 2.4% thin retroprosthetic	Article is a compilation of 4 cases reports, data from a non-controlled clinical trial and a literature review – as such would include patients already mentioned. Authors note that corneal melts were found to be associated with history of ocular herpes simplex infection. Change in protocol noted by authors.

Study details	Key efficacy outcomes	Key safety outcomes	Comments
grafts. Mean follow up: 16 months (range 0.6–51 months)	26 devices are in situ (63.4%) 4 devices have been removed (9.8%) and replaced with a second device. 11 devices (26.8%) have been removed and replaced with a donor graft. 27 cases (65.9%) have more than one year follow-up and the probability of device survival in this cases is 80%.	membrane • 4.9% thick retroprosthetic membrane • 2.4% problem retroprosthetic membrane (associated with melt) • 4.9% retinal detachment (tractional/diabetic)	
Hicks et al (2003) [3] 45 patients 35 patients (78%) had not received MPG. Mean follow up: 28.4 months. 10 patients (22%) had received MPG for 12 months Mean follow up 9.7 months.	**Not the aim of the study.**	**Incidence and timing of corneal stromal melting.** **Untreated** 12/35 (34%) developed a melt. Mean onset 8.8 months **Treated**: 6/10 (60%) developed a melt. Mean onset 23.2 months Total: 18/45	Study purpose: to evaluate the effect of topical medroxyprogrestrone (MPG). Treatment was halted because drug was not approved as an adjunctive treatment. Part of a larger trial.
Abbreviations: PL/LP perception light ; CF (counting fingers), HM (hand movements), BCVA (best corrected visual acuity); (HSV) herpes simplex infection			

Validity and generalisability of the studies

- Limited information is available on this procedure at present, and the majority of research on this procedure has been undertaken by one study group.
- From the initial phase I human trial of this procedure [4] through to the most recent report [5] there has been a change in device name and a change in protocol. The change in protocol relates to patient selection (the authors note that a history of herpes simplex infection is now considered a contraindication for the procedure) and the medication given to patients (patients were originally given medroxyprogestrerone MPG but this treatment was halted because the drug was not approved as a adjunctive treatment).
- Consequently the more recent papers present separately the results for non-herptic and herptic patients.
- Patient selection would seem to be important for this procedure and most of the papers report clear inclusion and exclusion criteria.
- However, in some of the papers deficiencies lie in the reporting of outcomes, that is the quality of reporting. In one paper particularly [1] the text and figures are difficult to reconcile.
- The outcome of visual acuity was in general not well reported and it was unclear whether this outcome had been assessed by an independent person.
- Patient results may be presented in more than one paper given that one paper [5] is a compilation of 4 cases reports, data from a non-controlled clinical trial and a literature review.

Specialist Advisors' opinions

- There are few procedures available for corneal blindness when corneal grafts have failed, this is one such procedure with a good short-term record.
- Relatively few patients are suitable for this procedure.
- Patients require long-term follow up.
- Uncertainty about the long-term success rates, however data is being collected on all cases.
- It will be important to know the mid-term to late complications rate following this procedure.

Issues for consideration by IPAC

- Procedure can be repeated or reversed.
- The manufacturer maintains a registry.

References

1 Hicks CR, Crawford GJ, Lou X, Tan DT et al. Corneal replacement using a synthetic hydrogel cornea, AlphaCor: device, preliminary outcomes and complications. *Eye* 2003; 17(3):385–92.

2 Hicks CR, Crawford GJ, Tan DT, Snibson GR et al. Outcomes of implantation of an artificial cornea, AlphaCor: effects of prior ocular herpes simplex infection. *Cornea* 2002; 21(7):685–90.

3 Hicks CR, Crawford GJ. Melting after keratoprosthesis implantation: The effects of medroxyprogesterone. *Cornea* 2003; 22(6):497–500.

4 Crawford GJ, Hicks CR, Lou X, Vijayasekaran S et al. The Chirila Keratoprosthesis: phase I human clinical trial. *Ophthalmology* 2002; 109(5):883–9.

5 Hicks CR, Crawford GJ, Tan DT, Snibson GR et al. AlphaCor trade mark Cases: Comparative Outcomes. *Cornea* 2003; 22(7):583–90.

Appendix A: Studies not included in the summary tables

Study Details	Patients/ follow up	Comments
Hicks C, Crawford G, Chirila T, Wiffen S et al. Development and clinical assessment of an artificial cornea. *Progress in Retinal & Eye Research* 2000; 19(2):149–70.	6	Does not add to the evidence base
Hicks C, Crawford G, Chirila T, Lou X et al. Pilot study of the Chirila Keratoprosthesis in human patients. *An Inst Barraquer (Barc)* 2001; 30:109–11.	7 implants	Brief report, refers to the above report
Crawford G, Hicks C, Chirila T, Lou X. Pro I: an overview. *An Inst Barraquer (Barc)* 2002; 2002(31):155–6.	12 patients	Very brief abstract type report
Tan D, Crawford G, Hicks C, Lou X, et al. Chirila KPro II: Case Histories. *An Inst Barraquer (Barc*) 2002; 31:157–8.	3 patients 2–6 months	Very brief abstract type report
Hicks C, Crawford G, Chirila T, Tan D. Pro III: keratoprosthesis or not? *An Inst Barraquer (Barc)* 2002; 31:159–60.	Not applicable	Review paper
Hicks CR and Crawford. Indications and technique: AlphaCor artificial cornea. *Techniques in Opthalmology*, 2003;	Not applicable	In press
Hicks CR, Chirila TV, Werner L, Crawford GJ, et al. Deposits in artificial corneas: risk factors and prevention	Not applicable	Submitted for publication
Eguchi H, Hicks CR, Crawford GJ et al Cataract surgery with AlphaCor	Not applicable	Submitted for publication

Appendix B: Literature search

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PredMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

#	Search History
1	cornea.mp. or exp CORNEA/
2	prostheses.mp. or exp "Prostheses and Implants"/
3	1 and 2
4	hydrogel.tw.
5	artificial.tw.
6	(hicks c or hicks cr).au.
7	4 or 5
8	3 and 6
9	3 and 4
10	9 and 5
11	alphacor.tw.
12	chirila.tw.
13	8 or 10 or 11 or 12