

Clinical outcomes after innovative lamellar corneal transplantation surgery

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CHAPTER 14

Valorization



Knowledge valorization refers to implementation of scientific knowledge for social or economic use or by making knowledge for new products, services, system and research.

For many years, full thickness penetrating keratoplasty (PK) was the gold standard treatment for various corneal diseases. In PK, the recipient full-thickness corneal tissue is replaced with full-thickness donor corneal tissue. The goals of PK were visual rehabilitation, tectonic support, reduction of pain, prevention of infection and cosmetic restoration. The leading indications were keratoconus, pseudophakic bullous keratopathy, Fuchs' endothelial dystrophy and regrafts. Other less common indications were post-infectious scarring, diverse corneal dystrophies, perforating corneal injury or chemical burns.¹

During the years 1998-2001 (prior to starting this thesis research) the percentage of donated eye tissue in the Netherlands issued for corneal grafting decreased from 50.8% (1998) to 35.2% (2001). In 2001 the Cornea Bank N.O.R.I. Amsterdam processed 2955 donor eyes of which 1040 were actually grafted. The major reasons for the discard rate of 64.8% of donated eye tissue were abnormalities of the anterior corneal stroma and a decreased vitality of the corneal endothelium. The shortage of donor tissue had resulted in an average waiting time for corneal transplantation of 6 months.

Lamellar corneal transplantation techniques that only transplant the anterior side of the cornea (deep anterior lamellar keratoplasty, DALK) or the posterior side (endothelial keratoplasty, EK) may use previously discarded tissue by transplantation of only the healthy part of the donated corneal tissue. The use of DALK and EK may lead to a more efficient use of donor material and could theoretically decrease the discard rate of donor tissue and shorten the waiting time. In the current thesis, we studied the clinical outcomes of innovative lamellar corneal transplantation surgery versus PK in a randomized multicenter clinical trial. Further, economic evaluation had been performed between lamellar keratoplasty (DALK and EK) versus PK.

In this chapter of valorization, we discuss the practical implications of the presented studies and the impact at the social and economic level.

In about 30% of keratoplasty cases, the indications are corneal pathologies with a normal endothelium. The most common indication is keratoconus. Endothelial allograft rejection was one of the most important reasons for graft failure in these patients. The main clinical aim to develop DALK was to preserve the endothelial layer, and to leave Descemet's membrane and the endothelium intact, thus eliminating endothelial allograft rejection. In the study of Borderie et al. the median predicted graft survival was

49.0 years in the DALK group and 17.3 years in the PK group.² Therefore, the need for re-transplantation will be less in DALK patients as compared to PK patients.

In this thesis the mean age of DALK and PK group is 43 years, and the most common indication for DALK is keratoconus. In these young patients visual impairment has a impact on their social and financial life since they are not able to perform the normal daily working activities. Our cost-effectiveness analysis showed that during the first year, the mean total costs per patient were €7607 in the DALK group and €6552 in the PK group.³ Costs differences were related mainly to the transplantation procedure and the additional surgical procedures. The higher costs regarding the transplantation procedure can be explained by the technically challenging and time-consuming big-bubble technique that is used in the DALK group, which increases the time needed for surgery as compared with PK. DALK is both more expensive but also more effective than a PK procedure. However, this study was done with a follow-up of 1 year, and it could be argued that long-term costs are higher in PK patients because of higher risk of graft failure and need for re-transplantation.

The main complication of the DALK technique is intraoperative rupture of Descemet's membrane, which required conversion to PK during the DALK procedure. This means that most corneal surgeons will order a donor cornea that is suitable for both DALK and PK. So the concept of using a donor cornea with low endothelial cell density is not widely accepted. More effective use of donor corneas in PK patients can be achieved by further surgical improvements in order to reduce risk of perforation.

In our study we showed that visual acuity was improved after DALK or PK procedure, but the costs were also very high. In cases of keratoconus, which is the most common indication for surgery, corneal crosslinking treatment had been described to stop the progression of the keratoconus. A randomized clinical trial with 3 years follow-up showed that corneal crosslinking was effective to stabilize the progression.⁴ In 2014, the Dutch Zorginstituut Nederland (ZiNL) decided that epi-off corneal treatment is in line with current standards of care and science and therefore is a treatment option for progressive keratoconus and should be reimbursed by all health insurances.

In the Netherlands, the cost of corneal crosslinking is around €1500 which is much lower than the cost of corneal transplantation. Long term analysis is needed to determine whether corneal crosslinking will be capable to decrease the need for corneal transplantation in keratoconus patients. Further, it is important for ophthalmologist, optician or eye care professional to diagnose progressive keratoconus in an early stage and to refer patients timely for corneal crosslinking.

For many years, PK has been the gold-standard technique for corneal transplantation resulting from endothelial disease or endothelial dysfunction. In recent years, in the USA and Europe, EK constitutes for about 45-50% of all transplant procedures. The major advantage of EK is that no sutures are required to keep the donor tissue in place, thereby preventing high irregular astigmatism and suture related events, resulting in faster visual rehabilitation and better wound stability.⁵

In EK, different techniques have been developed for the preparation of the donor cornea. Several techniques have been described in order to harvest donor lenticules for EK. The manual lamellar dissection techniques was not very popular due to the amount of technical challenges. Subsequently, the use of an automated microkeratome and a Femtosecond laser were reported for preparation of the donor lenticule.⁶

In our study, we showed the feasibility of the Femtosecond laser to prepare a standardized posterior lamellar lenticule for EK. The clinical outcome of our randomized study showed lower postoperative astigmatism and absence of wound healing related problems in the group of patients after Femtosecond laser-assisted Descemet's stripping endothelial keratoplasty (FS-DSEK).⁷ However, visual acuity is lower as compared to the conventional PK, and there was a high percentage of endothelial cell loss.

The results of our cost-effectiveness analysis between FS-DSEK, PK and Descemet's stripping automated endothelial keratoplasty (DSAEK) showed that FS-DSEK was not cost-effective compared to PK and DSAEK.⁸ DSAEK, on the other hand, was more costly but also more effective. The costs within 1 year follow-up were higher in EK patients, but it could be argued that long-term costs are lower and long-term effects are higher as compared to PK, because of the effects of suture removal in the PK group and a reduced risk of complications in the EK groups, with fewer hospital visits and emergency surgical interventions to be expected. However, long-term follow-up is needed to evaluate this potentially positive effect on the long-term cost-effectiveness of EK.

Due to the lower visual outcomes and higher costs of FS-DSEK, the Femtosecond laser technology is not widely used for the preparation of donor lenticules for EK. Currently, DSAEK is the most popular EK procedure and the donor lenticules were prepared with an automated microkeratome. In the beginning the donor lenticules were prepared by the surgeon in the operating room during the surgery. Recently, cornea banks in the Netherlands are able to supply pre-cut donor cornea for DSAEK or Descemet's membrane endothelial keratoplasty (DMEK). This can significantly lower the mean costs per patients for the preparation of the lamellar disks. Further, it will avoid the risk of tissue

loss during the stromal separation step in the surgery room, and the time needed for surgery has also decreased by approximately fifty percent.

With the automated microkeratome placed at the cornea bank it is now possible to use donor corneas with abnormalities of the anterior stroma and good corneal endothelium for EK procedures. This can lead to more donor corneas available for transplantation, a reduction of discard rate, and a shorter waiting list.

Several studies have shown that thickness of the donor lenticule is correlated with better visual acuity.^{9, 10} In the Netherlands, a randomized multicenter study is now evaluating the clinical outcomes between ultrathin (UT)-DSAEK and DSAEK. The preliminary results showed that the visual outcomes are significantly better in the UT-DSAEK group (personal communication with R.M.M.A. Nuijts, MD, PhD). Further, several studies have shown faster and better visual rehabilitation after DMEK compared to DSAEK.¹¹ As far as we know, there is no randomized clinical trial that has evaluated the clinical outcome of DMEK versus UT-DSAEK. The DMEK procedure is at this moment not accepted as standard treatment by ZiNL because it is not yet in line with current standards of care and science. Further randomized clinical research is needed to compare DMEK with UT-DSAEK, and long-term follow up is required to analyze graft survival.

In summary, this thesis presents the clinical outcomes and cost effectiveness of lamellar keratoplasty with the golden standard treatment PK. DALK is a promising surgical technique, but further surgical improvements are needed to be widely accepted. In cases of endothelial dysfunction, the EK procedure is now the first choice of surgical treatment. Nowadays, cornea banks in the Netherlands can provide pre-cut donor corneas and donor cornea with good corneal endothelium and abnormality of the anterior corneal stroma can now be used for EK procedure.

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