Corneal transplantation activity in Catalonia, Spain, from 2011 to 2018: Evolution of indications and surgical techniques

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Abstract

Purpose
To report corneal transplantation activity carried out in Catalonia (Spain) and the evolving indications for keratoplasty over an 8-year period.

Methods
Annual reports from the Catalan Transplant Organization, Spain, on corneal graft indications and techniques from 2011 to 2018 were reviewed.

Results
A total of 9457 keratoplasties were performed in Catalonia, from January 2011 to December 2018. The most frequent indications were bullous keratopathy (BK; 20.5%), Fuchs endothelial dystrophy (FED; 17.9%), re-graft (13.7%), and keratoconus (11.3%). Penetrating keratoplasty (PKP) accounted for 63.4% of all performed keratoplasties. Since the introduction of eye bank precut tissue for Descemet stripping automated endothelial keratoplasty (DSAEK) in 2013 and for Descemet membrane endothelial keratoplasty (DMEK) in 2017 the number of endothelial keratoplasties has drastically increased. An increasing trend of posterior lamellar techniques over the total of keratoplasties was found (p<0.001). Endothelial keratoplasties for different endothelial diseases indications (BK, FED, and re-graft), also showed an increasing trend (p<0.001). DMEK is the technique with the highest increase (statistically significantly different from linearity) over other endothelial keratoplasties in FED (p<0.001) but not in BK (p = 0.67) or re-grafts (p = 0.067).

Conclusion
Endothelial diseases represented the top indication for keratoplasty over the 8-year period. PKP is still the most used technique in Catalonia, but endothelial keratoplasties and especially DMEK showed a significant increasing trend over the last years. This is congruent with
the main rationale nowadays for keratoplasties: to customize and transplant as less tissue as possible. Therefore, the availability of precut tissue could have definitely enforced such approach.

Introduction

Corneal grafts are one of the most frequent transplanted tissues in the world [1]. In addition, keratoplasty techniques, and therefore indications, have majorly changed these last years, thanks to the upraise of selective corneal surgeries that have vastly improved visual recovery results. However, epidemiology on such surgeries is not always easy and mostly depends on regional eye bank report services. Moreover, several studies suggest most surgeons tend to customize indications and even perform more posterior lamellar techniques when eye bank precut tissue is available [2,3].

In 1989 the Spanish National Transplant Organization (Organización Nacional de Trasplantes–ONT) started its activity coordinating organ and tissue donations in Spain. In 1994, the autonomous region of Catalonia, started its own organization (Organització Catalana de Trasplantaments–OCATT), and joined efforts with ONT [4]. However, keratoplasty indications, techniques and trends have not been studied in depth since the introduction of precut corneal tissue supply by the main regional eye bank in such a population with a high volume of transplantations, 1000 keratoplasties/year on average, representing 25% to 30% of total keratoplasties in Spain. Over the last few years, the number of keratoplasties has increased in Spain (over 4000 keratoplasties/year since 2016, and even more in Catalonia [5].

In Catalonia, retrieval of ocular tissue is mainly performed by transplant coordinator teams and centralized by an eye bank (Barcelona Tissue Bank, BTB) [6]. Then, the ocular tissue is processed and distributed. The OCATT collects information on tissue viability and distribution from the different transplant centres, and surgical and clinic details and keratoplasty technique indications from standardized questionnaires sent to surgeons. Moreover, OCATT has a biovigilance system to detect adverse events and adverse reactions.

Being a centralized eye bank in Catalonia, BTB supplies corneal grafts and offers precut tissue for posterior lamellar techniques. In 2013, it started to supply precut tissue for Descemet Stripping Automated Endothelial Keratoplasty (DSAEK), and from 2017, precut tissue for Descemet Membrane Endothelial Keratoplasty (DMEK) was distributed [6]. Despite few surgeons started to perform endothelial keratoplasties (EK) before 2013, from that date, more and more surgeons dared to switch to posterior lamellar techniques due to the availability of precut tissue [3].

This study investigates the evolving trends of corneal transplantation from 2011 to 2018 in Catalonia centres, and its relationship with precut tissue supply.

Materials and methods

This study is a retrospective review of corneal tissue activity records of the OCATT in Catalonia, between January of 2011 and December of 2018. The included data corresponded to corneal tissue retrieved and implanted in Catalonia. ONT website was consulted to obtain data regarding the Spanish registries [5]. Institutional Ethics Committee Board approval was obtained for donor data revision (approval number HCB/2015/0879, Hospital Clinic de Barcelona, amended on 14th November of 2018). Research methods and analysis plan adhered to the Tenets of the Declaration of Helsinki. Data related to ocular tissue, its traceability, and
potential adverse events were treated in accordance with the appropriate European Union directives (2004/23/EC, 2006/17/EC, and 2006/86/EC). Patient data were encoded for management in accordance with the Spanish legislation on personal data protection (RD05/2018).

Reported data outcomes included, as per every year, number of cases in all surgical techniques as well as number of cases in each approach by their main clinical indication for keratoplasty. Descriptive results are presented as absolute frequencies and percentages for categorical variables. Linear trends (Mantel-Haenszel statistic) and deviation from linearity were obtained. All tests were performed with a two-sided type I error of 5% with the statistical package STATA v.15.1 (StataCorp, College Station, Texas, USA).

## Results

Between 2011 and 2018, 9457 keratoplasties were performed in Catalonia, that is 1182 keratoplasties/year on average (ranging 989–1456 per year) (Fig 1A). To report how prevalent or frequent are transplants among regions or countries, the unit transplants per million population (pmp) is commonly used. In this regard, 190.2 corneal transplants per million population and year were performed on average in Catalonia (Fig 1A), while this figure was 80.4 pmp/year on average in Spain (Fig 1B).

Together with the corneal tissue sample, a follow-up form is sent to the surgeon, asking for adverse events, surgical technique, and surgery indication, among others. Despite the high

![Figure 1](https://doi.org/10.1371/journal.pone.0249946.g001)

**Fig 1.** Number of keratoplasties per year carried out in Catalonia (1A) and corneal transplants per million inhabitants in Catalonia and Spain (1B).
recommendation to send it back, the response rate per year was heterogeneous, ranging from 59.4% to 96%. Information about surgical indication and keratoplasty technique was obtained from 7660 out of 9457 procedures (80.9%). The indications for corneal transplantation are listed in Table 1. The most frequent indications were bullous keratopathy (BK; 1574; 20.5%), Fuchs endothelial dystrophy (FED) and other endothelial dystrophies (1373; 17.9%), re-graft due to endothelial failure (1051; 13.7%), and keratoconus (865; 11.3%).

Corneal transplantation techniques performed from 2011 to 2018 were: penetrating keratoplasty (PKP; 4848; 63.4%), deep anterior lamellar keratoplasty (DALK; 827; 10.7%), and endothelial keratoplasty (1985; 25.9%). During the years 2011 and 2012, due to the low number of posterior lamellar keratoplasties performed, no distinction between DMEK and DSAEK was formally made. Evolving trends in keratoplasty techniques over years are shown in Fig 2A.

The evolving trend of lamellar techniques was statistically analysed and resumed in Table 2. It showed statistically significant increasing trends of endothelial and anterior lamellar keratoplasties, which differ from linearity in almost all reported associations but for DMEK performed on BK, given the low number of cases. In addition, although DMEK showed an increasing trend in re-grafts, it did not reach statistical significance (p = 0.067) (Fig 2B).

**Discussion**

Catalonia is an autonomous region of Spain with 32108.2 km² and a population of 7.5 million people at end of 2018 [7]. The number of corneal transplants performed in Catalonia from 2011 to 2018 has been 9457 (average of 1050.7 keratoplasties/year), corresponding to 190.2 corneal transplants per million population and year performed on average, while this figure is 80.4 on average in Spain. In other words, 32.7% of all keratoplasties performed in Spain were performed in Catalonia [5]. Currently, the BTB is the only bank in Spain that processes corneas for precut tissue delivery [8].

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of transplants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullous keratopathy secondary to surgery (any)</td>
<td>1574 (20.5)</td>
</tr>
<tr>
<td>Fuchs endothelial dystrophy</td>
<td>1373 (17.9)</td>
</tr>
<tr>
<td>Re-graft due to endothelial failure</td>
<td>1051 (13.7)</td>
</tr>
<tr>
<td>Keratoconus/ectasia (other than post-refractive)</td>
<td>865 (11.3)</td>
</tr>
<tr>
<td>Infection (viral, fungal and bacterial)</td>
<td>604 (7.9)</td>
</tr>
<tr>
<td>Corneal degeneration</td>
<td>563 (7.3)</td>
</tr>
<tr>
<td>Chemical injury/trauma</td>
<td>381 (5.0)</td>
</tr>
<tr>
<td>Congenital opacity</td>
<td>225 (2.9)</td>
</tr>
<tr>
<td>Ulcerative keratitis (non-infectious)</td>
<td>221 (2.9)</td>
</tr>
<tr>
<td>Stromal corneal dystrophy</td>
<td>213 (2.8)</td>
</tr>
<tr>
<td>Refractive surgical complication</td>
<td>50 (0.7)</td>
</tr>
<tr>
<td>Other*</td>
<td>540 (7.0)</td>
</tr>
<tr>
<td>Total of transplants with diagnosis informed</td>
<td>7660 (100)</td>
</tr>
<tr>
<td>Total of transplants</td>
<td>9457</td>
</tr>
</tbody>
</table>

*Other included: Rejection (134; 1.75%), regraft for a reason other than endothelial failure (78; 1%), oedema of unknown origin (67; 0.9%), irregular astigmatism (22; 0.3%), opacification (14; 0.18%), perforation (9; 0.12%), toxic epidermal necrolysis (7; 0.09%), descemetocoele (5; 0.06%), pemphigoid (4; 0.05%), Peters anomaly (2; 0.03%), congenital glaucoma (1; 0.01%), bacterial keratitis and perforation (1; 0.01%), epithelial ingrowth (1; 0.01%), hematocornea (1; 0.01%), unknown (194; 2.5%).

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As observed, the most usual indication for corneal transplantation during the period of study was BK followed by FED. The most prevalent technique was PKP, which accounted for 63.4% of all performed keratoplasties. A statistically significantly increasing trend of posterior lamellar techniques over the total of keratoplasties was found. In addition, DMEK was indeed the technique with the highest increase over other endothelial keratoplasties in FED but not in BK or re-grafts due to endothelial failure. That increase could be associated to the start of pre-cut tissue supply for EK by the regional corneal tissue bank. Therefore, a predominance of the lamellar techniques is expected to be found in the next years. Interestingly, such a shift has already happened in other countries several years earlier than in the studied area: PK replaced by lamellar keratoplasties was first reported in 2015 in the United States [9] and 2017 in Germany [10] and a significant shifting trend was stated in 2014 in Canada [11,12] and 2015 in Italy; [13] while in other areas this shift had not been detected so far [14].

Indications for corneal transplantation are still different from one region to another, despite overall trends are indeed changing and converging: BK and FED have been seen to be most common indications for transplant in developed countries whereas infective keratitis and scars are more common in developing countries [11,15–17]. However, BK may represented...
the second indication—after FED [9,11,12,18] or keratoconus [19,20]—and even the third one [10]. Intrinsic methodological issues such as questionnaire codification—for example FED with oedematous cornea could be eventually codified as BK—could explain that finding over the sole fact of a lower prevalence of FED in that geographical area per se.

Keratoplasty nowadays sticks to the rationale of transplanting as less tissue as possible in order to avoid allograft rejection, reduce postoperative complications and increase graft survival rates. Among endothelial techniques, DSAEK receptors often have a hyperopic shift and, in some cases, suboptimal visual recovery [21–23] while DMEK is a more anatomically accurate procedure that just replaces Descemet membrane and endothelium, potentially leading to a faster and better visual recovery with minimal refractive change [24–27]. Therefore, DMEK could be considered as the intended common-practice technique for corneal endothelial disease but, however, its widespread adoption is limited due to the overall challenging surgical technique in addition to the relative difficulty of donor tissue preparation [2,25].

The availability of precut tissue for DSAEK started in Catalonia in 2013, which representing a breakthrough in EK surgical indication [6]. This shift was even more important after the introduction of precut tissue for DMEK in 2017 [6]. Some studies [3] have already highlighted an increased trend to perform EK after precut tissue introduction. It is commonly thought that surgeons are more prone to perform posterior lamellar techniques when the risk to damage corneal tissue—due to manual preparation—is very low [28,29]. Previous reports have shown no differences in best corrected visual acuity, central corneal pachymetry or complications—dislocations, primary graft failure—found between corneas prepared by the surgeon in the operating room and precut tissue for DSAEK [29–31] or even DMEK [32]. Other advantages of precut tissue are the lower rate of microbiological culture positivity and lower risk of receptor infection [33,34]. Despite that, some areas still favour DMEK technique regarding indications over DSAEK even without precut tissue [10]. Taking into consideration all these facts and figures we are prone to presume that in the next few years DMEK trend in Catalonia will continue its increase thanks to precut tissue, among other reasons. Despite that, the increasing trend in lamellar techniques used in Catalonia has turn up late compared to other countries: for example, in 2011 in Catalonia only 19% of BK were treated with EK whereas in Columbia

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### Table 2. Increasing trends of different techniques globally and for different pathologies (over total of keratoplasties with available information).

<table>
<thead>
<tr>
<th>Technique analysed</th>
<th>n/total analysed</th>
<th>% in 2011 (2013 for DMEK, in italics)</th>
<th>% in 2018</th>
<th>Increasing trend</th>
<th>Different from linearity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall keratoplasties (2011–2018)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EK over total of keratoplasties</td>
<td>1985/7660</td>
<td>9.8</td>
<td>36.0</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>EK in endothelial diseases</td>
<td>1825/4003</td>
<td>2.0</td>
<td>54.9</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>EK in BK</td>
<td>588/1576</td>
<td>19.0</td>
<td>29.9</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>EK in FED</td>
<td>999/1377</td>
<td>43.2</td>
<td>92.0</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>EK in re-grafts</td>
<td>228/1030</td>
<td>4.1</td>
<td>36.7</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>DALK over total of keratoplasties</td>
<td>827/7660</td>
<td>6.8</td>
<td>12.2</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>DALK in ectasia and KC</td>
<td>359/865</td>
<td>23.6</td>
<td>59.4</td>
<td>p&lt;0.001</td>
<td>p = 0.0129</td>
</tr>
<tr>
<td><strong>Overall EK (2013–2018)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMEK over EK</td>
<td>563/1835</td>
<td>7.4</td>
<td>43.8</td>
<td>p&lt;0.001</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>DMEK over EK in BK</td>
<td>96/513</td>
<td>2.6</td>
<td>29.5</td>
<td>p&lt;0.001</td>
<td>p = 0.67</td>
</tr>
<tr>
<td>DMEK over EK in FED</td>
<td>376/938</td>
<td>11.8</td>
<td>52.7</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>DMEK over EK in re-grafts</td>
<td>50/214</td>
<td>10.0</td>
<td>27.6</td>
<td>p = 0.067</td>
<td>NA</td>
</tr>
</tbody>
</table>

EK: Endothelial keratoplasty; DMEK: Descemet membrane endothelial keratoplasty; BK: Bullous keratopathy; FED: Fuchs endothelial dystrophy; NA: Non-applicable; KC: Keratoconus.

*Endothelial diseases: BK, FED, and re-graft due to endothelial failure.

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(Canada) this proportion corresponded to 57.7%; [11] in the United States of America, about 50% of all corneal transplants are indeed EK according to the Eye Bank Association of America [9,35] while in this study that figure only accounted for 9.7%. Moreover, in Italy, an increasing trend of posterior lamellar techniques was found between 2002 and 2008 whereas in our area it happened after 2013 [13]. Other authors have investigated the keratoplasty activity in different centers in Spain [36,37]. As in their conclusions, we found than PKP was still the most prevalent technique used globally during the period of study despite the advantages described in literature of EK over PKP [21,23,25].

Even though being based on solid and official data on tissue transplantation, this study has still some limitations to disclose. First, as it is based on the OCATT’s annual reports, data is kept subject to surgeons’ responses accuracy. In other studies, preoperative diagnosis reported by surgeons ranged from 50% to 97% [9,38]. Surgeons must be aware of the importance of returning follow-up forms in order to increase exactness of reports. In addition, starting of any supply procedure, such as corneal precut tissue, can present with logistic problems such as bureaucracy issues or temporal shortage; therefore, data on usage of such supply could have been underestimated.

Generally, EK have shown several determinant advantages over PKP such as better visual acuity outcomes, less rejection rate and better postoperative recovery, despite being technically more difficult and having a higher learning curve [15,39,40]. These proven benefits in many prevalent indications and the extended use of eye bank precut tissue are thought to be the main causes of the increasing trend of both EK as a whole and DMEK in particular in our area. Given these characteristics in the next few years we could expect EK to drastically outperform PKP in endothelial corneal disease. On the other hand, and for similar reasons, we could also presume an overall EK major shift towards DMEK accordingly. In-depth epidemiological studies as the presented one would be mandatory in the years to come to follow-up and evaluate tissue transplantation trends.

**Author Contributions**

**Conceptualization:** Noelia Sabater-Cruz, Ricardo P. Casaroli-Marano.

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**References**


