Making Better Keratoplasty Decisions for Acanthamoeba Keratitis: A Meta-analysis

Leying Wang
Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University

Zhenyu Wei
Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University

Kai Cao
Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University

Xizhan Xu
Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University

Zijun Zhang
Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University

Qiankun Chen
Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University

Qingfeng Liang (lqflucky@163.com)
Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University

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Abstract

Acanthamoeba keratitis (AK) is a blinding disease with increasing incidence. Keratoplasty is the common therapy method for AK; however, the suitable times and types of keratoplasty for AK remains unclear. These systemic review intended to assess the outcomes of AK undergoing different keratoplasty procedures. Literature searches were conducted in Pubmed, EMBASE, Web of Science, and the Cochrane. Eleven studies with 216 eyes were included. The meta-analysis showed optical keratoplasty had better best corrected visual acuity (BCVA), higher graft survival rate, lower recurrence and multiple keratoplasties rate than therapeutic keratoplasty. The occurrence rate of postoperative complications were similar between optical keratoplasty and therapeutic keratoplasty. The AK patients performed therapeutic keratoplasty within 5 months of AK onset had significant better final BCVA than those who after 5 months of AK duration. Moreover, therapeutic deep anterior lamellar keratoplasty (TDALK) reserved better BCVA than therapeutic penetrating keratoplasty (TPK). The eyes performed TPK were prone to need multiple keratoplasties than those with TDALK. These results suggested optical keratoplasty was superior to therapeutic keratoplasty in AK patients. The drug-resistant AK patients should be underwent therapeutic keratoplasty promptly, especially within 5 months of AK onset. TDALK was a preferable therapeutic keratoplasty option for AK patients where possible.

Introduction

Acanthamoeba keratitis (AK) is a relatively uncommon but potentially blinding corneal infection. During the past 40 years, the incidence of AK increases dramatically with the growing popularity of contact lens wearing.[1,2] This problem is further exacerbated by the high misdiagnosis rate of AK because of nonspecific symptoms and signs.[3,4] Moreover, the response to AK drug therapy can be disappointing.[5] Increased morbidity, delayed diagnosis and poor medical effect will contribute to the high keratoplasty rate (11.1%-53%) and more AK patients need corneal transplantation.[4,6,7]

Currently, there is no international agreement on AK therapy and the prognosis of keratoplasty for AK was underperformance.[8] The timing of keratoplasty in AK remains controversial. Some studies suggested that optical keratoplasty performed on non-inflamed eye after medically cured AK had better prognosis than therapeutic keratoplasty.[1,9] However, other reports presented optical keratoplasty might have more complications due to long-term intensive drug therapy and corneal neovascularization.[10] In therapeutic keratoplasty, although the lesions were eradicated and the therapy duration was shorten, there was a higher risk of recurrence due to wandering trophozoite in the cornea.[11] An inflamed eye was also prone to graft rejection.[12]

The optimal timing of therapeutic keratoplasty surgery needs to be carefully considered to plan. Should therapeutic keratoplasty be performed only in AK cases with pending corneal perforation or limbus involving? On the contrary, timely therapeutic keratoplasty may prevent the involvement of peripheral cornea, but the risk of recurrence is potentially high. Furthermore, the two surgery options, therapeutic penetrating keratoplasty (TPK) and therapeutic deep anterior lamellar keratoplasty (TDALK), are alternative. TPK avoids residual acanthamoeba in the deep host cornea. TDALK lower the risk of endothelial rejection. Therefore, this study compares the prognosis of different types and times of keratoplasty in AK patients, focusing on final best corrected visual acuity (BCVA), graft survival, AK recurrence and postoperative complications.

Methods

Search Strategy

The following databases were searched: Pubmed, EMBASE, Web of Science, and Cochrane to identify relevant studies. The listed below search terms were used: “(Amoeba or Amoebae or Acanthamoeba or Ameba) And (Cornea or Keratitis) And (Medication or Drug or Operation or Therapy)”. Non-English articles were excluded. The publication date was from the creation of the databases to September 5, 2021.

Eligibility Criteria

The prospective or retrospective interventional cohorts, case series, noncomparative studies, nonrandomized comparative or randomized clinical trials were considered. The clinical studies that involved fewer than 5 eyes or without clinical outcomes were excluded. Literature reviews, animal studies, correspondence, notes, editorials, and conference abstracts were also excluded. To compare the outcomes between optical keratoplasty and therapeutic keratoplasty, the studies were included only when the outcomes of the two procedures were reported separately. To compare the effectiveness of early and late therapeutic keratoplasty, the studies were included only when the exact preoperative disease duration and final BCVA of every patient were provided. For comparison of TPK and TDALK, studies that reported detail clinical outcomes were included. If multiple publications were reported from the same institutions, only the latest study with a larger number of patients were included.

Quality Assessment of Studies

The quality of each cohort study was evaluated by the modified Newcastle-Ottawa Scale.[13] Two authors (L.W and Z.W) assessed the quality independently. In cases of disagreement, a third author (Q.L) was asked to reach a consensus.

Data Extraction

The data was extracted by the two authors (L.W and Z.W) independently. The following demographic and clinical data from each study was collected: study design, sample size, demographic characteristics, preoperative BCVA, surgery type and follow-up time. The outcomes extracted from studies contained preoperative BCVA, final BCVA, graft survival rate, AK recurrence rate, multiple keratoplasties rate, and postoperative complications (ocular hypertension, glaucoma and cataract, etc).

Statistical Analysis

All the analysis were conducted with the open-source R program (Version 3.4.4). Study heterogeneity was assessed using the Q test and I^2 statistic. Robust Meta-analysis techniques were used to draw the change in clinical outcomes and complications after optical keratoplasty and therapeutic keratoplasty.[14] Local polynomial regression was used to fit the curve and calculate the inflection point of therapeutic keratoplasty timing. The t test, the chi-square test and Fisher’s exact test were used to compare the difference of clinical outcomes and complications between early and late therapeutic keratoplasty, TPK and TDALK. $p < 0.05$ was set as the limit of statistical significance.

Results

Literature Search

The original electronic database search confirmed 1518 nonduplicate articles, of which 1457 did not meet the inclusion criteria. The remaining of 61 full-text articles were reviewed. Eleven studies were included totally. The analysis was divided into 3 parts to compare different types and times of keratoplasty (Fig. 1). For comparing optical and therapeutic keratoplasty, 4 studies (126 eyes) with the outcomes of the 2 types of keratoplasty respectively were included for meta-analysis. Four studies with 49 eyes which reported the therapeutic keratoplasty timing, preoperative and postoperative BCVA of each patient were analyzed to determine optimal keratoplasty timing. For comparing TPK and TDALK, 2 of the above 8 studies were excluded because they performed TPK or TDALK for AK patients, and the outcomes of the 2 types of keratoplasty could not be extracted separately. The remaining 6 studies performed TPK and the other 3 studies underwent TDALK were analyzed to conclude the better operative option.

Characteristics of Included Studies

Details of included meta-analysis studies and comparative analysis studies were shown in Table 1 and Table 2. All the included studies were retrospective and single center studies. A total of 216 eyes of 216 patients were included for analysis. The age, gender and follow-up time were similar among the different types of keratoplasty (all $p > 0.05$). The preoperative disease duration was 5–70 months in optical keratoplasty and 1–23 months in therapeutic keratoplasty for meta-analysis, 0.66-36 months in patients included for therapeutic keratoplasty timing decision, and 1–2 months in TDALK group.

Table 1
Characteristics of the studies included in the OKP and TKP meta-analysis. Abbreviations: OKP, optical keratoplasty; TKP, therapeutic keratoplasty.

Author	Publish year	Country	Sample size (n)		Age (years)		Preoperative disease duration (mo)		NOS Quality score
			OKP	TKP	OKP	TKP	OKP	TKP	
Liu, H. Y et al.	2020	China	10	17	27.1 ± 1.5		-		6
Robaei, D. et al.	2015	UK	24	25	44.3 ± 16.6	43.0 ± 12.1	17.0 ± 3.38	7.0 ± 2.3	8
Kitzmann, A. S. et al.	2009	USA	9	22	30.0 ± 12.5	40.0 ± 14.0	19.0 ± 16.3	6.0 ± 5.5	7
Ficker, L. A. et al.	1993	UK	6	13	40.5		-		6

Table 2
Characteristics of the studies included for TKP timing and TDALK analysis. Abbreviation: TPK, therapeutic penetrating keratoplasty; TDALK, therapeutic deep anterior lamellar keratoplasty.

Author	Publish year	Country	Eyes (n)	Preoperative disease duration (months)	Preoperative BCVA	Mean follow-up time (months)	Final BCVA	NOS quality score
TPK								
Laurik, K. L.	2019	Germany	23	6.96 ± 7.19	1.73 ± 0.48	27 ± 19.4	1.32 ± 1.57	6
Roozbahani, M.	2019	USA	12	5.17 ± 2.21	2.07 ± 1.00	15 (3–50)	1.83 ± 1.16	6
Tanhehco, T.	2010	USA	8	2.94 ± 1.83	2.2 ± 1.07	19.4 (7.03–39.6)	1.26 ± 1.21	5
Butler, T. K.	2001	Australia	6	5.33 ± 5.00	1.66 ± 1.05	35.5 ± 22.6	0.425 ± 0.27	6
TDALK								
Antonio D. Z.	2021	Italy	7	-	-	-	0.06 ± 0	4
Bagga, B.	2020	India	23	-	-	5 (1.4–11.4)	1.79 (0.70–2.78)	6
Sarnicola, E.	2016	Italy	11	1–2 (range)	1.3-3	24.8 ± 9.6	0.84 ± 0.14	6

Clinical Outcomes of Optical Keratoplasty and Therapeutic Keratoplasty Meta-Analysis

Comparing with the therapeutic keratoplasty group, the final BCVA in optical keratoplasty group was better (0.90±,1.22 vs.0.52 ± 0.55, $p < 0.001$; Fig. 2). The AK recurrence rate was 4.1% in optical keratoplasty group, which was significantly lower than that in therapeutic keratoplasty group (25.6%, $p = 0.034$). The overall graft survival rate was 66.2%, and that of optical keratoplasty was significantly higher than therapeutic keratoplasty (92.0% vs. 53.8%, $p = 0.017$). Besides, the proportion of patients who need multiple keratoplasties was significantly lower in optical keratoplasty group than that in therapeutic keratoplasty group (8.2% vs. 39.7%, $p = 0.003$; Fig. 2). No quantitative analysis was performed for preoperative BCVA, because only 1 study clearly reported this information.[15]

In terms of postoperative complications, the occurrence rate of ocular hypertension was higher after therapeutic keratoplasty than that after optical keratoplasty (38.5% vs. 21.7%, $p = 0.132$). Moreover, patients performed therapeutic keratoplasty had a higher rates of glaucoma surgery and cataract surgery than patients treated with optical keratoplasty (14.3% vs 0%, $p = 0.305$: 20.0% vs. 13.3%, $p = 0.580$). But the difference of optical keratoplasty and therapeutic keratoplasty did not reach statistically significant in the above 3 complications (supplementary Fig. 1).

Comparison of Early and Late Therapeutic Keratoplasty

Overall, 45 patients with detailed period of therapeutic keratoplasty were included in the analysis.[6,11,16,17] All of them were treated with penetrating keratoplasty. The median preoperative disease duration was 5 months (range: 0.66-36 months). A strong relationship was shown between preoperative diseases duration and final visual acuity (r = 0.47, $p = 0.001$). The curve fitting model shown the inflection point was 5 months, which means the final BCVA significant changed at the point (Fig. 3). Further, the patients were categorized into early therapeutic keratoplasty group (preoperative disease duration ≤ 5 months; n = 24) and late therapeutic keratoplasty (preoperative disease duration 5 months; n = 21). The preoperative BCVA was similar between early and late therapeutic keratoplasty (2.24 ± 1.00 vs. 2.38 ± 1.08; $p = 0.68$). Nevertheless, the final BCVA was 0.86 ± 1.07 in early therapeutic keratoplasty, which was significantly better than late therapeutic keratoplasty (1.86 ± 1.70; $p = 0.023$).

Comparison of TPK and TDALK

A total of 6 studies with TPK (84 eyes) and 3 studies with TDALK (41 eyes) were included.[6,11,15–21] Final visual was significantly better in TDALK group than that in TPK group (0.54 ± 0.38 vs. 1.34 ± 0.54; $p = 0.008$). Compared with TPK group, the graft survival rate was higher, and the AK recurrence rate was lower in TDALK group, but the differences were not statistically significant (65.8% vs. 76.5%, $p = 0.44$; 26.3% vs. 8.8%, $p = 0.075$). Furthermore, the patients performed TPK were prone to need multiple keratoplasties significantly (31.0% vs. 4.8%; $p = 0.019$; Fig. 3).

Discussion

This study suggests that optical keratoplasty is the best choice for AK patients whenever possible, which has better final BCVA and safety. Early keratoplasty is critical to AK cases with poor response to medical treatment and timely therapeutic keratoplasty within 5 months would be recommended. TDALK should be considered prior when taking therapeutic keratoplasty. Penetrating keratoplasty could be performed when corneal perforation and deep stroma involvement.

The meta-analysis showed that optical keratoplasty has better final BCVA, higher graft survival rate and less recurrence rate than therapeutic keratoplasty for AK patients. Besides, optical keratoplasty and therapeutic keratoplasty had similar incidence rate of postoperative complications. Thus, optical keratoplasty was the preferred type of keratoplasty for AK patients. These conclusions were in tune with numerous publications that the infection should be treated medically and the keratoplasty should be performed on uninflamed or controlled-inflamed AK if possible.[10,16,22] The optical keratoplasty was defined as least 1–3 months after discontinue antiamoebic therapy.[10,23,24] Of note, limbal stem cell deficiency (LSCD) was easily induced in AK patient who experienced long-term inflammation and medical therapy, which could result in graft failure. Thus, it is very important to diagnose and treat LSCD before optical keratoplasty. Moreover, optical lamellar keratoplasty was preferred to lower the risk of endothelial rejection due to corneal neovascularization and previous corneal inflammation.[10]

When AK did not response well to medication, an early therapeutic keratoplasty was proposed. The included studies considered the following symptoms or signs were indicators for therapeutic keratoplasty: unrelieved

pain, decreased BCVA, expansion of stromal infiltrates, impending or actual corneal perforation and increased anterior chamber inflammation after at least 1 week intensive topical anti-amoeba therapy.[10,11,21] An interesting thing to note was the relevance and inflection point at 5 months in Fig. 3, which meant the longer the disease duration, the worse the final BCVA, and the patients who performed therapeutic keratoplasty after 5 months of AK had worse final BCVA. These results further supported the advice that the better opportunity for therapeutic keratoplasty is the first 5 months of AK duration.[25]

The major factors that affecting the outcomes between early and late therapeutic keratoplasty included the graft size and inflammatory response. Previous studies concluded the graft size was an powerful indicator for the ultimate anatomical and functional outcomes in infectious keratitis.[10,26,27] Meanwhile, late therapeutic keratoplasty usually meant long-term toxic medical therapy and persistent ulcer, which accompanied by severe inflammation and associated with postoperative complications, such as glaucoma, cataract, anterior synechiae and graft rejection.[16,26,28] However, how to use corticosteroid to control the inflammation before and after therapeutic keratoplasty in AK patients remain questionable. Some studies started steroids after therapeutic keratoplasty immediately, and some researchers used steroids at least 2 weeks after therapeutic keratoplasty.[10,16,26] A study reported FK506 might improve the graft success rate after therapeutic keratoplasty in AK patients.[29] Meanwhile, anti-amoebic agents must be continued postoperative for at least 2 months.[30] Clinicians must balance the relationship between anti-inflammation and anti-amoeba therapy, which dictate the success of keratoplasty.

TDALK has been proposed as an effective therapy for drug-resistant localized infectious keratitis. The currently study showed that the AK patients who performed TDALK had better final BCVA and who performed TPK were more likely to need multiple keratoplasties. Furthermore, a recent study concluded TDALK provided less high-order aberrations than TPK for AK patients.[19] Sarnicola et al. performed TDALK within 1–2 months after AK onset.[21] Early surgery might also play an important role in improving the prognosis. The potential risk of TDALK was the infection may not be eliminated completely. In the included studies, only 8.8% (3/34) patients had AK recurrence after TDALK, [20,21] which was like TPK. Besides, TDALK could also lower the risk of endothelial rejection. Hence, TDALK, instead of penetrating keratoplasty, should be considered first in medically unresponsive AK.

This study also had some limitations. First, there was no randomized clinical trial comparing different keratoplasty procedure in AK, which limited the evidence level of the study. Second, because of the limit reported information, the preoperative BCVA only compared between early and late therapeutic keratoplasty, but not between optical keratoplasty and therapeutic keratoplasty, TPK and TDALK. Third, considering only 1 study reported the complications of TDALK and none of the patients had complications, it is difficult to conduct the analysis of complications between TDALK and TPK. Forth, the better operation opportunity for TDALK could not be calculated based on current studies. Further studies with detail pre-TDALK and post-TDALK information should be needed.

In summary, this systemic review demonstrated the advantage of optical keratoplasty for AK patients. For those who poor response to anti-amoeba therapy, early therapeutic keratoplasty, especially deep anterior lamellar keratoplasty should be considered. Further adequately powered studies with preoperative and postoperative

details, including preoperative disease duration, anti-amoeba therapy duration, clinical signs etc., would be helpful in making the best keratoplasty decision comprehensively.

Declarations

Acknowledgement

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Author contributions

L.W was the major contributor in writing the manuscript. L.W and Z.W performed the literature review and data abstraction. K.C and X.X performed the statistical analyses. Z.Z and Q.C made a substantial contribution to the revision of the manuscript. Q.L was primarily responsible for the study design and revision of the paper.

Data availability statement

All data relevant to the study are available from the corresponding author on reasonable request

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Figures

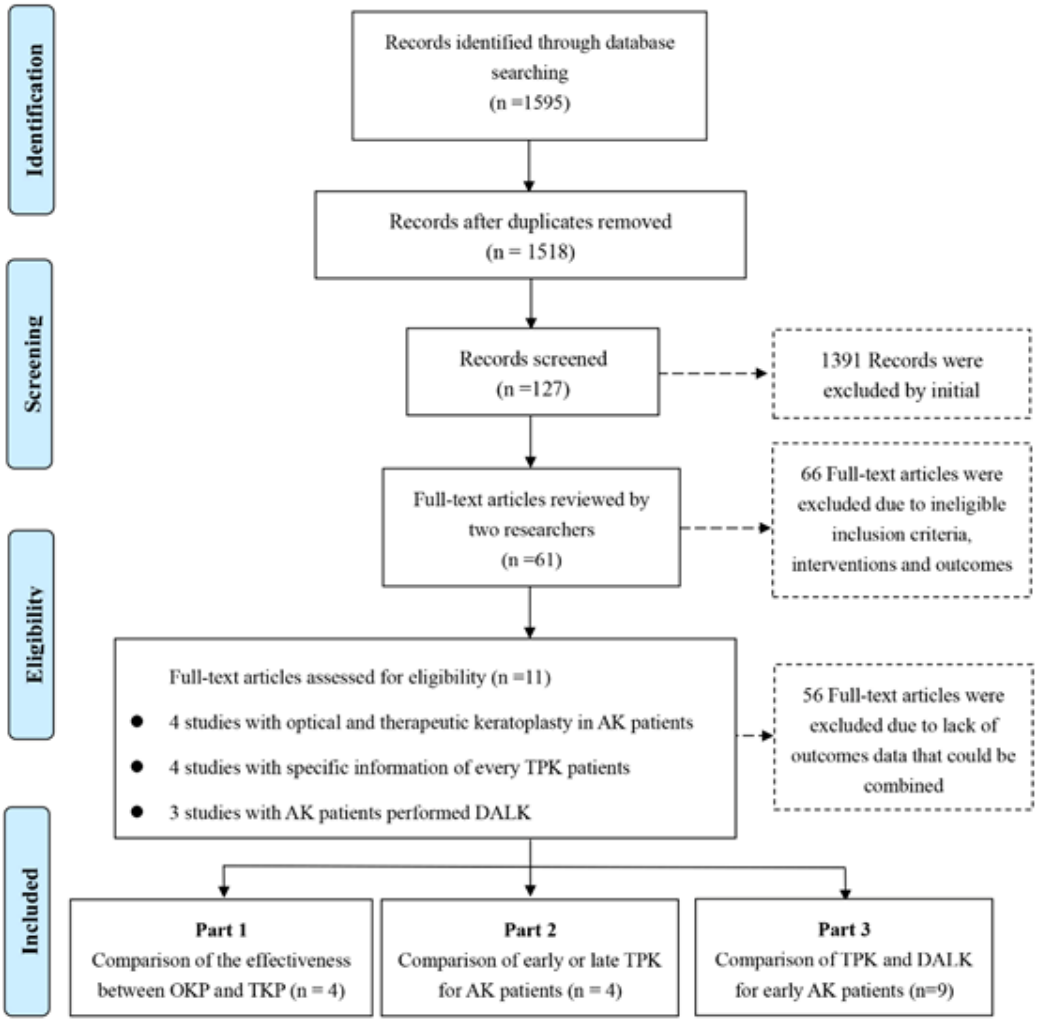

Figure 1

Flow chart of paper selection.

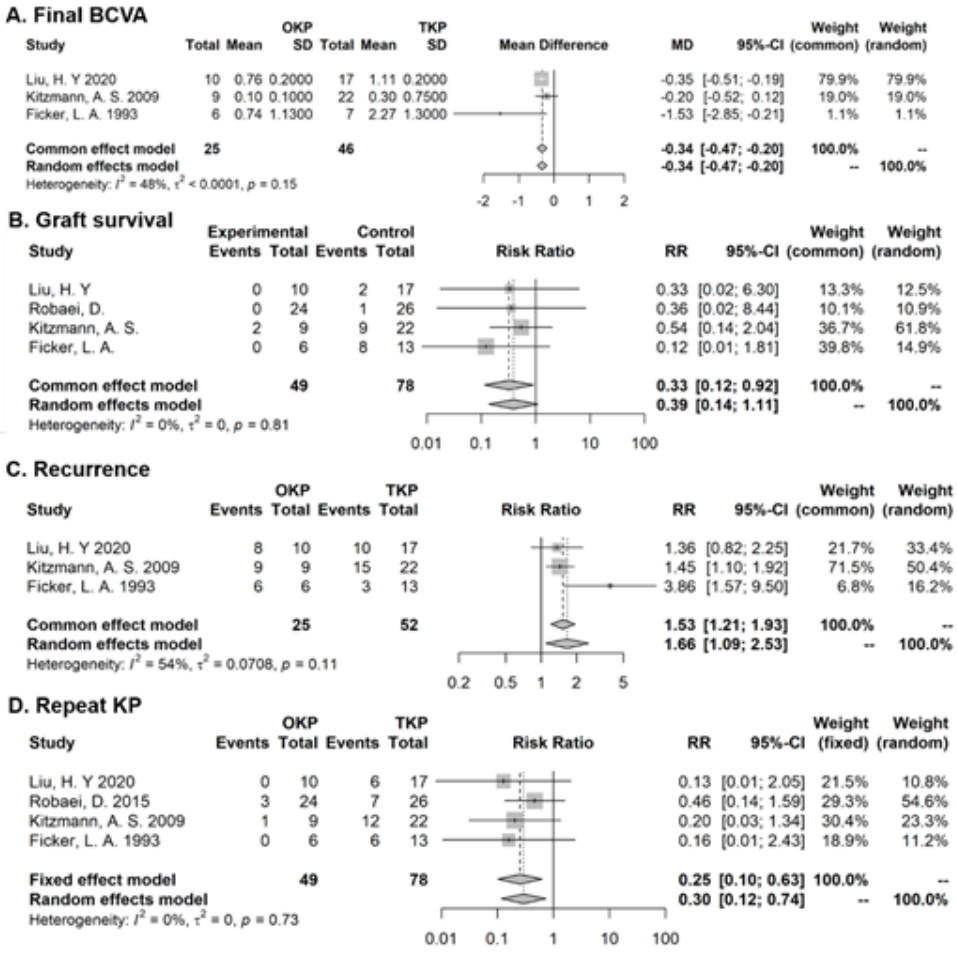

Figure 2

Forest plot for final BCVA and postoperative complications after optical keratoplasty and therapeutic keratoplasty. The final BCVA was better in optical keratoplasty than therapeutic keratoplasty (A). The rates of recurrence, graft failure and repeat keratoplasty were significantly higher in therapeutic keratoplasty than optical keratoplasty (B-D).

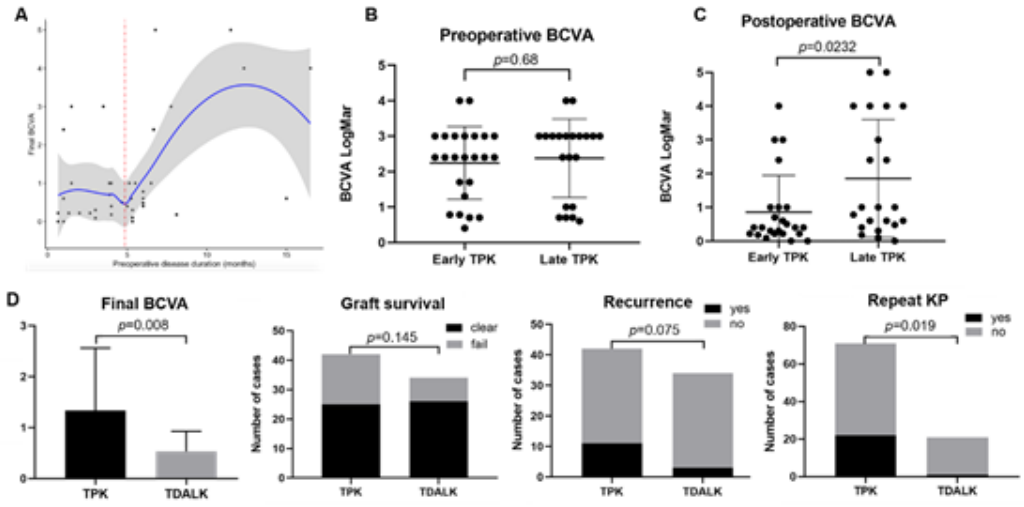

Figure 3

The relationship between preoperative disease time of therapeutic keratoplasty and final BCVA. (A) Regression analysis showed the preoperative disease time was significant related to final BCVA after therapeutic keratoplasty, with an inflection point of 5 months. (B) The preoperative BCVA was similar between early and late therapeutic keratoplasty. (C) The postoperative BCVA was superior in early therapeutic keratoplasty than late therapeutic keratoplasty. D showed the comparison of the surgical effect after TPK and TDALK. The final BCVA of TDALK was better than TPK. The graft failure rate and recurrence rate was similar between TPK and TDALK. The rate of multiple keratoplasties was significantly higher in TPK group than that in TDALK group.

Supplementary Files

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- Supplementaryfigure1.docx