• Letter to the Editor •

Combined Descemet stripping automated endothelial keratoplasty and intravitreal dexamethasone implant for concomitant pseudophakic bullous keratopathy and cystoid macular edema

Gabriella Cirigliano, Marco R Pastore, Alberto A Perrotta, Chiara De Giacinto, Daniele Tognetto

Eye Clinic, Department of Medical Surgical Sciences and Health, University of Trieste, Ospedale Maggiore, Trieste 34129, Italy

Correspondence to: Marco R Pastore. Eye Clinic, Department of Medical Surgical Sciences and Health, University of Trieste, Ospedale Maggiore Piazza Ospitale 1, Trieste 34129, Italy. marco.pastore@hotmail.it

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Dear Editor,

Endothelial cell density decreases with age and in various ocular conditions, including corneal endotheliitis, uveitis, pseudoexfoliation syndrome, and birth injury[1]. The reduction of endothelial cell density is exacerbated over time after intraocular surgery[1]. Descemet stripping automated endothelial keratoplasty (DSAEK) is considered the primary procedure for patients with only endothelial dysfunction. Compared to penetrating keratoplasty, this selective approach has several advantages in terms of more rapid visual rehabilitation, less surgically-induced astigmatism, less incidence of graft rejection, and preservation of biomechanical properties[2].

Pseudophakic cystoid macular edema (PCME) is still recognized as one of the most common causes of poor visual outcome following uneventful cataract surgery[3]. The incidence of clinical PCME following modern cataract surgery is reported as 1.17%-4.04%[3]. The great variance of incidence can be explained by the presence of diabetes, co-pathologic features, and intraoperative complications. The dexamethasone implant is considered an effective treatment option for patients with Irvine-Gass syndrome, even in cases with a longer edema duration and in pretreated or refractory cases[3]. Ozurdex™ (Allergan, Inc., Irvine, CA, USA) is a biodegradable sustained-release intravitreal implant of 0.7 mg dexamethasone in the NOVADUR (Allergan, Inc., USA) solid polymer drug delivery system[4].

A 68-year-old man with no significant past medical history underwent uncomplicated phacoemulsification surgery in the left eye with in-the-bag intraocular lens (IOL) implantation. One month after surgery his visual acuity (VA) improved to 20/20 with a clear cornea and no macular optical coherence tomography (OCT) alteration. Five months later, he was referred to a tertiary eye hospital for metamorphopsia and progressive visual impairment. Although the slit-lamp examination revealed a normal anterior segment, at fundus evaluation a yellowish macular reflex was detected. Fluorescein angiography (FA) and spectral-domain OCT (SD-OCT; Spectralis HRA+OCT, Heidelberg Engineering, Heidelberg, Germany) demonstrated a late onset PCME (Figure 1). Non-steroidal anti-inflammatory drugs (NSAID) treatment with topical bromfenac 0.09% (Yellox, Bausch & Lomb, Zug, Swiss) was introduced. Six weeks later, VA improved to 20/25 and a complete PCME resolution was observed. According to the 'on-off' phenomena related to the cessation and new resumption of the therapy[3], a recurrent PCME was noted one month after the end of NSAID treatment. A topical bromfenac 0.009% was reintroduced with no reduction in macular thickness. Despite the supplementary treatment with topical nepafenac 0.3% (Nevanac®, Alcon Laboratories, Inc., Fort Worth, TX, USA) for four weeks, no additional benefit was detected and the VA decreased to 20/63 for concomitant pseudophakic bullous keratopathy (PBK) developing. An informed consent for a combined DSAEK and intravitreal dexamethasone implant (Ozurdex, Allergan Inc., Irvine, CA, USA) was obtained. The treatment was performed according to the Italian Bioethical Legislation and followed the Declaration of Helsinki. At the preoperative evaluation, a normal intraocular pressure (IOP) of 14 mm Hg was detected and the *in vivo* confocal analysis demonstrated an endothelial cell count of 615 cells/mm^2. Although is not recommended

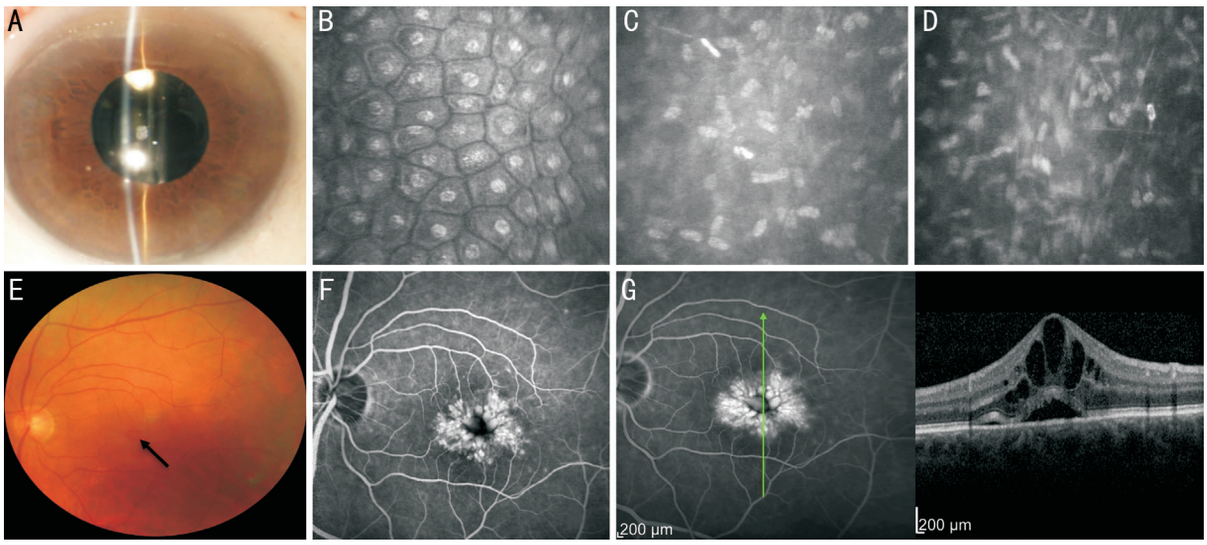

Figure 1 Left eye preoperative evaluation of concomitant pseudophakic bullous keratopathy and cystoid macular edema A: Slit-lamp photos of bullous keratopathy due to endothelial injury after cataract surgery; B-D: *In vivo* confocal micrographs, showing endothelium (B) posterior (C) and anterior stroma (D) images [ConfoScan 4, Confocal Microscope (Nidek, Inc., Freemont, CA, USA)]; E: Colour fundus imaging reveals a pathological yellowish reflex in macular area, corresponding to cystoid macular edema; F: FA at middle frames demonstrated intense foveal eakage with cystoid intraretinal exudation and subfoveal neurosensorial detachment reported at combined mid/late FA and SD-OCT (G).

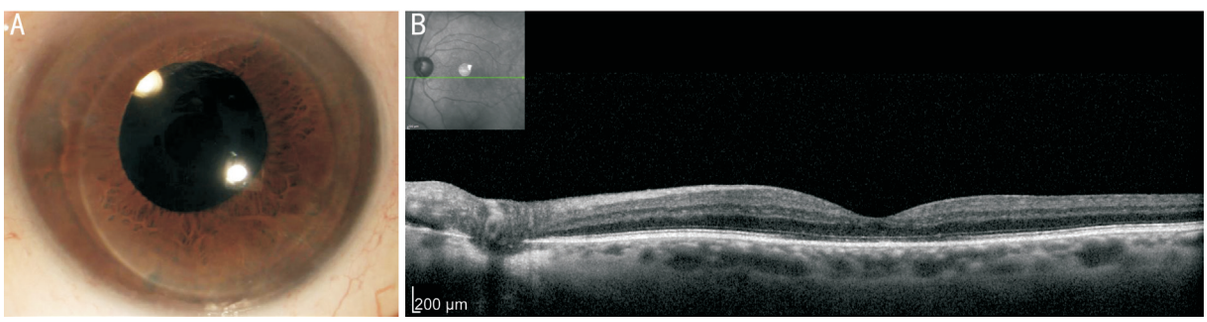

Figure 2 Nine months follow-up of combined Descemet stripping automated endothelial keratoplasty and intravitreal dexamethasone implant A: Both the donor and the host corneas were clear at slit-lamp photograph examination; B: Combined infrared and SD-OCT show the complete regression of the intraretinal and subretinal exudation, resulting in a integrity of photoreceptors ellipsoid zone and a good VA.

for steroid implant, a peripheral iridectomy (PI) during DSAEK was performed in order to avoid a pupillary block. Dexamethasone 0.15% and ofloxacin 1.5% eye drops were topically administered 4 times a day, with a stepwise decrease in three weeks during the follow-up.

Postoperatively, VA was 20/40, the graft was clear and *in situ*, and the IOL was central and stable. The PCME was completely resolved four weeks after the intravitreal Ozurdex implant and VA improved to 20/32 (Figure 2). During the nine-month follow-up, none adverse event and PCME recurrence was reported. No IOP spikes were observed with a transient increasing up to 18 mm Hg two months after the steroid implantation. At *in vivo* confocal examination, postoperative endothelial cell count was 2085, 1973, 1924, 1879 cells/mm^2, at 1, 3, 6, and 9mo, respectively.

In most cases PCME spontaneously resolve. Only a small percentage reaches a clinical relevance and need therapeutic treatments. As Zur and Loewenstein[3] reported, topical administration of NSAIDs and steroid has been demonstrated as a good strategy in the management of PCME. Although injection of periocular corticosteroids or systemic treatment are viable options for macular edema refractory to topical treatment, intravitreal steroids implants were shown to be the highly effective and useful solution.

Ozurdex® (Allergan, Inc., USA) is a biocompatible sustained-release intravitreal implant (measures 6 mm in length and 0.46 mm diameter) of 0.7 mg dexamethasone over up 6mo. It doesn't need to be retrieved and can be repeatedly administered. The use of Ozurdex® implant for the intravitreal treatment of macular edema associated with noninfectious posterior uveitis was approved for the first time in 2009[4].

Cataract formation and transient IOP increasing are the main ocular side effects reported after intravitreal steroids insert[4]. The pathogenic conditions related to steroid-induced ocular hypertension is not yet fully understood. A trabecular meshwork dysfunction may lead to the outflow alteration. The

increased extracellular deposits, the inhibition of trabecular meshwork cell function and cytoskeleton rearrangement play a key role in the pathogenic mechanism[5].

The corneal decompensation due to Ozurdex wandering into the anterior chamber (AC) represents one of the most serious complications after the dexamethasone implant[6-18]. The mechanism of endothelial decompensation could be related to drug toxicity or direct mechanical trauma by the implant[18]. According to all cases reported in literature[6-14], a PI, a damaged or absent posterior lens capsule, and previous vitrectomy, are the main risk factors for Ozurdex migration into the AC. However, the presence of any of those risk, does not necessarily mean that passage will occur[6].

To promptly manage both corneal and retinal diseases, we decided for combined DSAEK and intravitreal dexamethasone implant for concomitant PBK and PCME. Previous studies reported the presence in the corneal stroma of subepithelial fibrosis and keratocytes transdifferentiated into fibroblasts or myofibroblast in patients with bullous keratopathy[15-16]. A common factor related to the expression of these pathological changes was found to be the duration of stromal edema, which can lead to the development of Descemet's folds and reduced postoperative VA after DSAEK[17]. Related to these pathological structural alterations an early surgical timing must be considered.

Furthermore, an early treatment of the PCME in order to restore the microstructural level of the photoreceptor inner segment-outer segment junction integrity results in a better final VA and reduce the progression to chronic recurrent stage of the PCME[3]. To the best of our knowledge, none previous similar combined procedure was reported in literature.

Whereas no history of prior vitrectomy and not damaged posterior lens capsule with uncomplicated phacoemulsification and in-the-bag IOL implantation was reported in the past medical history, we decided to perform an reduced size inferior PI during the corneal endothelial keratoplasty procedure to avoid the pupillary block and to reduce the IOP spike after the air bubble injection into the AC. In addition to these early postoperative conditions, pre-existing glaucoma and topical steroid use are considered the most common causes of elevated IOP after DSAEK[18]. In this report, none IOP spikes or the Ozurdex wandering into the AC were detected during the 9-month follow-up[19].

As reported by Pedemonte-Sarrias *et al*[20], cystoid macular edema is the most common posterior segment complication after DSAEK alone (7%) and responds to standard therapy for pseudophakic syndrome. It appears to be more frequent when concurrent with phacoemulsification (21%). The concomitant the sustained-released intravitreal dexamethasone implantation prevent this possible complication and, in addition, allow for the reduction of topical steroid administration in postoperative management.

In our opinion, in selected non-vitrectomized eyes without damaged or absent posterior lens capsule, combined DSAEK and dexamethasone intravitreal implant could be considered an effective treatment option for the management of cataract surgery complicated by concomitant PCME and PBK.

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