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Corneoconjunctival transposition for the treatment of deep stromal to full-thickness corneal defects in dogs: A multicentric retrospective study of 100 cases (2012-2018)

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Abstract

Objective: To describe and evaluate the use of corneoconjunctival transposition (CTT) as a surgical treatment for canine deep stromal ulcers, descemetoceles, and full-thickness corneal defects and to determine its efficacy in preserving corneal graft transparency and vision.

Animals studied: One hundred client-owned dogs with deep stromal ulcers, descemetoceles, or full-thickness corneal defects.

Methods: Medical records of canine patients that underwent CCT, from 2012 to 2018, were reviewed. Only, patients with preoperative positive consensual pupillary light and dazzle reflexes were included.

Results: There were 59 males and 41 females, from 0.3 to 17 years. Brachycephalic breeds were overrepresented (65%). All patients were unilaterally affected, with 16 deep stromal ulcers, 33 descemetoceles, and 51 corneal perforations, of a median (range) size of 4 (2-8) mm. The central cornea was affected in the majority of cases (57%), and euryblepharon and keratoconjunctivitis sicca were the most common concurrent ocular diseases (42% and 40%, respectively). The graft was most frequently harvested from dorsal (67%), and 9/0 absorbable suture material was used. Intraoperative and postoperative complications were seen in 7 and 21 cases, respectively. Mean follow-up time was 107.8 days. Vision was preserved in 96% patients, with 62% showing faint to mild opacification. Among the statistically analyzed variables, euryblepharon and pigmentary keratitis were found to be significantly associated with greater corneal graft opacification ($P = .040$ and $P = .028$, respectively).

Conclusions: Corneoconjunctival transposition is an effective surgical treatment for deep stromal, descemetocele, and full-thickness corneal defects in dogs, achieving a highly satisfactory degree of corneal graft transparency and preserving vision.

KEYWORDS

autograft, cornea, corneal surgery, graft rejection, keratoplasty, visual outcome

1 | INTRODUCTION

Corneal ulceration occurs commonly in canine patients, and its treatment depends mainly on the type of ulcer/defect. The most common causes for corneal ulcers in dogs include trauma, foreign bodies, infection, inadequate lacrimal secretion, corneal endothelial dysfunction, spontaneous, toxic, and anatomic/functional abnormalities in adnexa.[1,2] As complicated deep corneal defects (where there is a loss of more than half of the corneal thickness) or corneal perforations are serious conditions that may result in devastating visual consequences, these must be managed with intensive treatment to preserve the anatomic integrity of the cornea and to prevent complications such as endophthalmitis, secondary glaucoma, and/or subsequent blindness. Medical treatment for deep corneal defects (deep stromal ulcer and descemetocele) ideally should consist of as often as hourly topically applied medication for the first 24-48 hours at least. Despite the intensive topical/systemic treatment, the corneal stroma has a limited ability to regenerate and when successful, corneal healing by secondary intention may induce an important fibrovascular response causing excessive scarring of the affected site.[2] Therefore, as medical treatment is often insufficient for the effective and rapid repair of a deep corneal defect, or when there is a corneal perforation, surgery is considered the initial gold-standard treatment. Reported techniques include fresh or frozen lamellar[3-5] or penetrating[4,6] keratoplasty, tissue adhesive,[7] synthetic grafts and biomaterials,[1,8-13] conjunctival flaps,[14-18] and amniotic membrane of different origins.[19-21] However, there are limitations in their application, as some techniques are not always effective when perforations are larger than 3 mm in diameter, others have a higher immunologic rejection rate, and many of them induce a moderate to severe opacification of the affected area.[1,3,9,10,20]

Corneoscleral transposition (CST), firstly described in veterinary medicine by Parshall et al[22] in 1973, is a type of autogenous graft that uses a sliding pedicle of cornea and attached sclera to repair corneal defects. Corneoscleral transpositions have undergone several modifications over time, and nowadays, it has become more common the usage of corneoconjunctival graft (CCT) instead. Bearing in mind that this technique provides an "autologous" graft and avoids potential risk for donor tissue rejection, it grants numerous benefits when compared with keratoplasties. Among those benefits are shorter healing time, less intensive postoperative topical and systemic treatment, and less scarring.[22] These characteristics are of vital importance as the main goals of any corneal treatment, apart from the tectonic support, are to preserve or improve the quantity and quality of light entering the eye.[2] Since its description, CST-CCT have been only reported as a treatment modality for feline corneal sequestra.[23-25] To the authors' knowledge, there are no publications evaluating CCT as a treatment option for deep corneal defects/corneal perforations in the dog. The aim of the present study was to describe CCT for treatment of deep stromal ulcers, descemetoceles, and full-thickness corneal defects in dogs, and to determine the visual outcome and corneal graft transparency.

2 | MATERIALS AND METHODS

2.1 | Animals and data collection

Medical records of dogs that underwent CCT for the treatment of deep stromal ulcers, descemetoceles, or full-thickness corneal defects at the Veterinary Teaching Hospital of the Autonomous University of Barcelona (Bellaterra, Spain), Willows Veterinary Centre and Referral Service (Solihull, UK), Vetoeiras Hospital Veterinário (Oeiras, Portugal), Optivet Referrals (Havant, UK), and Eye Clinic Visionvet (San Giovanni in Persiceto, Italy), from 2012 to 2018, were reviewed.

Special attention was given to breed, age, gender, concurrent ocular diseases, affected eye, location and size of the corneal defect (central vs paracentral; in mm), graft direction and size (in mm), intra and postoperative complications, postoperative treatment, follow-up time (in days), and assessment of vision (through menace response), and corneal graft opacification (CGO) at last visit.

2.2 | Ophthalmic examination

All dogs underwent a complete and bilateral ophthalmic examination by either a board-certified veterinary ophthalmologist or resident-in-training, including Schirmer tear test I, neuro-ophthalmic examination (menace response, dazzle, and pupillary light reflexes), biomicroscopy (Kowa SL-15/SL-17®, Kowa Company Ltd.), rebound tonometry (TonoVet®, Icare Finland Oy), indirect funduscopic examination (Heine Omega 500®, Heine), and fluorescein test. Only, patients with positive consensual pupillary light and dazzle reflexes in the affected eye were included in the study.

2.3 | Anesthetic and presurgical protocol

Preoperative topical medication varied, as it depended on the treatment regimen used by the referring veterinarian and the clinical phase of the disease prior to referral. Once admitted, all patients were administered systemic antibiotics and NSAIDs. The anesthetic protocol was elected depending on the veterinary center. The periocular skin and ocular surface were aseptically prepared with povidone iodine solution diluted in 1:50 saline, except for corneal perforations, in which case only saline was used. The patient was positioned in dorsal recumbency with the muzzle tilted vertically so that the

surface of the iris would be parallel to the floor. Intravenous neuromuscular blocking agents (atracurium 0.2 mg/kg IV) were used to achieve central positioning of the eye, when needed.

2.4 | Surgical procedure

All surgeries were performed by a board-certified veterinary ophthalmologist or a resident-in-training under direct supervision. In full-thickness corneal defects, sodium hyaluronate viscoelastic solution was used whenever necessary to restore anterior chamber depth and to eliminate synechiae. Corneal defects were measured using a Castroviejo caliper, and the patient's cornea was surgically prepared by excising all necrotic and collagenolytic tissue, delineating the defect using a no. 64 Beaver blade, while preserving as much healthy corneal tissue as possible. When appropriate, excessive corneal bleeding was controlled with topical diluted epinephrine (1:1000). A sliding corneoconjunctival flap was prepared by completing two diverging linear incisions extending from the lesion to the limbus and into the bulbar conjunctiva, with one half to two thirds of corneal thickness depth, depending on the nature of the primary defect. The graft was preferentially harvested from the dorsal quadrant, unless a ventral or lateral defect indicated preparation with different and more accessible graft direction. Lamellar keratectomy was performed using a crescent blade knife, the conjunctival portion was dissected using Westcott scissors, and finally the limbus was sectioned using corneal scissors or the crescent blade knife. The corneoconjunctival graft was advanced over the defect, assuring that there was no tension once it was laid in place. When needed, it was further trimmed (with corneal scissors) to fit perfectly the corneal bed. In case of corneal perforation, the iris and fibrin plug were dissected from the cornea with the use of viscoelastic agents. Then, the leading and lateral margins of the graft were sutured in the corneal bed with absorbable 9-0 polyglycolic acid or polyglactin 910 in a simple interrupted and a continuous pattern, respectively. In some cases of euryblepharon, a bilateral medial canthoplasty was concurrently performed.

2.5 | Postoperative management

Postoperative treatment consisted of topical broad-spectrum antibiotics, NSAIDs, and artificial tears (3-6 times daily), as well as mydriatic/cycloplegic drugs (2-3 times daily). When concurrent KCS was diagnosed, topical administration of 0.2% cyclosporine A was started. All animals wore an Elizabethan collar and received systemic antibiotics and NSAIDs during the immediate postoperative period. Topical antibiotics and mydriatics/cycloplegics were discontinued when fluorescein test was negative at the margins of the corneal graft and no ocular discomfort was detected, normally 1-2 weeks postoperatively. In some cases, topical NSAIDs were interchanged with topical corticosteroid solutions to further reduce corneal scarring and neovascularization and then were progressively discontinued as transparency improved over several months postoperatively. Topical cyclosporine A was maintained as long-term treatment in the KCS affected dogs.

2.6 | Follow-up

The recommended initial follow-up protocol was at days 7, 21, and 45 post-surgery. The following controls depended on the evolution of each case. Nevertheless, this postoperative follow-up varied due to owners compliance, different referral protocol established by the veterinary hospital in question, and unpredictable postoperative complications.

Vision was assessed at last visit by means of a positive menace response and was classified as positive or negative. As previously described, CGO was graded as nearly transparent (grade 0), faint (grade 1), mildly (grade 2), moderately (grade 3), or severely (grade 4) opaque (Figure 1).[26] Corneal graft opacification grading was based on the clinical description present on the patients' record and on high-resolution digital photographic images. Gradings were performed by two observers closely familiarized with the grading score, and results data were pooled. Graft healing time was not evaluated as such, as the corneal epithelium was intact at the time of the surgery. Nevertheless, an approximate period of 3-4 weeks was stipulated necessary for complete integration of the corneal graft.

2.7 | Statistical analysis

Qualitative results were described by absolute and relative frequencies, and quantitative results by mean and standard deviation (SD), or median and 95% confidence interval (95% CI) and absolute range (minimum and maximum). All results where tabulate for whole cohort and for CGO grouped in grade 0-2 and grade 3-4, in order to facilitate clinical interpretation. Fisher's exact test was used for qualitative variables and Mann-Whitney U test for quantitative variables. A type I error of 5% and a commercial software (SPSS 25.0®, IBM) were used for all statistical analyses.

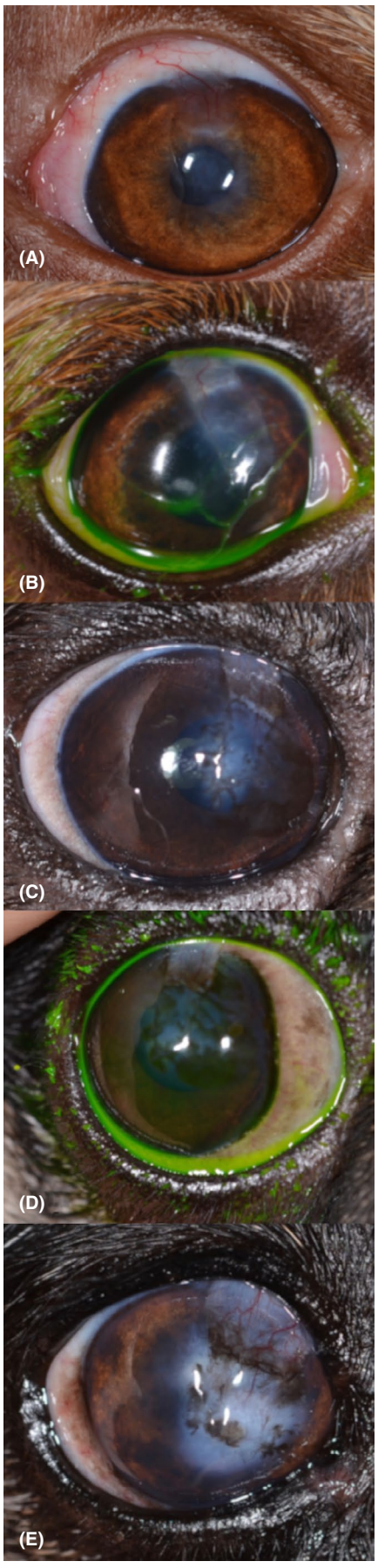

FIGURE 1 Corneal graft opacification (CGO) grading: (A) nearly transparent [grade 0; n = 1], (B) faint opaque [grade 1; n = 26], (C) mildly opaque [grade 2; n = 35], (D) moderately opaque [grade 3; n = 32], and (E) severely opaque [grade 4; n = 6]

3 | RESULTS

3.1 | Animals

One hundred dogs (100 eyes) met the inclusion criteria (Veterinary Teaching Hospital of the Autonomous University of Barcelona [n = 45], Willows Veterinary Centre and Referral Service [n = 23], Vetoeiras Hospital Veterinário [n = 13], Optivet Referrals [n = 11], and Eye Clinic Visionvet [n = 8]). Twenty-five different breeds were affected, being Pug, French Bulldog, and cross-breed dogs overrepresented (24/100 [24%], 23/100 [23%], and 15/100 [15%], respectively). There were 59 males (neutered 14/59) and 41 females (spayed 18/41) of a median age (95% CI) of 5 years (5;7), ranging from 0.3 to 17 years.

3.2 | Ophthalmic findings at first examination

All patients were unilaterally affected (53/100 [53%] right eye and 47/100 [47%] left eye). Full-thickness corneal defects were diagnosed in 51% of the cases (51/100), followed by descemetoceles in 33% (33/100) and deep stromal ulcers in 16% (16/100). The central cornea was the most commonly affected area (57/100; 57%), but defects were also located nasally (23/100; 23%), temporally (9/100; 9%), dorsally (7/100; 7%), and ventrally (4/100; 4%). The most common concurrent ocular diseases included euryblepharon (42/100; 42%), keratoconjunctivitis sicca (40/100; 40%), medial-inferior entropion (32/100; 32%), pigmentary keratitis (13/100; 13%), crystalline corneal deposits (11/100; 11%), and distichiasis (9/100; 9%). Other less frequent concurrent abnormalities included facial paralysis (3/100; 3%), superficial chronic corneal epithelial defects and palpebral laceration (2/100; 2% each), eyelid mass, nictitans gland prolapse, and nanophthalmia (1/100; 1% each).

3.3 | Size of corneal defect, surgery and corneal suture

All surgeries were performed by a board-certified veterinary ophthalmologist (95/100; 95%) or a resident-in-training under direct supervision (5/100; 5%). Whereas one case was a rescue procedure for a previously performed corneal graft, all other surgeries were the primary treatment for

the corneal defects. The size of the corneal defects ranged from 2 to 8 mm, with a median diameter (95% CI) of 4 mm (3;4), being less than 4 mm in 83% of the cases (83/100) and larger in 17% (17/100). Corneoconjunctival graft was performed mostly in a dorsal direction (67/100; 67%), although in cases in which this could not be achieved, other directions were used (from nasal or ventral [12/100; 12% each], and from temporal [9/100; 9%]). Suture material used was 9-0 polyglycolic acid (52/100; 52%) or polyglactin 910 (48/100; 48%).

Other concurrent surgical procedures performed in 15 patients (15/100; 15%) included as follows: medial canthoplasty (10/100; 10%), temporal tarsorrhaphy (3/100; 3%), and amniotic membrane graft (2/100; 2%)

Intraoperative complications were detected in seven cases (7/100; 7%). Perforation of the conjunctival portion of the graft (4/100; 4%) was the most frequently reported, followed by perforation of the limbus, inadequate size of the conjunctival portion of the graft, and intraocular hemorrhage (1/100; 1% each).

3.4 | Follow-up and postoperative complications

Mean (SD) follow-up time was 107.8 (143.3) days. Postoperative complications were detected in 21 cases (21%; 21/100): interrupted suture dehiscence (6/100; 6%), epithelial corneal ulcer and excessive granulation tissue formation (4/100; 4% each), graft retraction (3/100; 3%), corneal perforation (2/100; 2%), deep stromal ulcer (1/100; 1%), and keratomalacia (1/100; 1%). Surgical rescue treatment was necessary in three cases (3/100; 3%): two patients with graft retraction and 1 with corneal perforation. However, vision was maintained at last re-check in those patients.

3.5 | Corneal opacification assessment and vision outcome

Corneal graft opacification evaluation was based on the clinical description present on the patients' record for all the patients (100/100) and in high-resolution digital photographic images, when available (82/100; 82%). The corneal portion of the corneoconjunctival graft remained nearly transparent in 1 (1%), faint opaque in 26 (26%), mildly opaque in 35 (35%), moderately opaque in 32 (32%), and severely opaque in six dogs (6%) For statistical analyses, CGO was grouped from nearly transparent to mildly opaque (grades 0-2; 62%) and from moderately to severely opaque (grades 3-4; 38%) (Table 1). No statistically significant correlation was detected between CGO at last visit, regardless of its grade, and age, breed (brachycephalic vs mesocephalic/dolichocephalic), corneal defect location (central vs paracentral) or type (full-thickness vs descemetocele/deep stromal), graft size (0-4 mm vs > 4 mm), graft direction (from dorsal vs ventral/lateral/medial), suture material (polyglycolic acid vs polyglactin 910), visual outcome (positive vs negative menace response), and follow-up time ($P > .05$).

The effect of the most common concurrent ocular diseases on CGO was also assessed. The additional diagnosis of KCS, medial-inferior entropion, calcium or lipid corneal deposits, or distichiasis was not significantly correlated with the CGO at last re-check ($P > .05$). However, euryblepharon and pigmentary keratitis were found to be significantly associated with greater CGO ($P = .040$ and $P = .028$, respectively). Most patients affected by euryblepharon (42/100; 42%) and pigmentary keratitis (13/100; 13%) at first presentation showed moderately or severely opaque corneas after surgery (21/42 and 9/13, respectively); whereas, those with normal palpebral fissure length (58/100; 58%) and without corneal pigmentation (87/100; 87%) evidenced lower postoperative CGO (41/58; 41% and 58/87; 58%, respectively). Although medial canthoplasty was performed for surgical correction of euryblepharon in 8/42 affected cases (8%), no statistically significant improvement of CGO was observed ($P = .238$).

Menace response was assessed at last re-check, being classified as positive in 96/100 (96%) and negative in 4/100 (4%). Of the visual eyes, sixty-one (61/96; 63.5%) showed transparency or faint to mild opacification of the central cornea, whereas 35 eyes (35/96; 36.4%) had moderately to severely opaque corneal grafts (Figure 2).

4 | DISCUSSION

Deep stromal ulcers, descemetoceles, and full-thickness corneal defects are an ophthalmological emergency, threatening both vision and integrity of the patient's globe. Although multiple surgical techniques have been extensively described, to the authors´ knowledge, no published study has evaluated the use and success rate of corneoconjunctival transposition in dogs for the treatment of these ocular conditions. The present study focused on the use and outcome of CCT as treatment for 100 cases of deep and perforating corneal defects in canine eyes.

In canine ophthalmology, complicated deep corneal ulcers and corneal perforations have been historically treated using a variety of graft tissues such as homologous and heterologous corneal grafts,[3-6] amniotic membrane of different origins,[19-21] small intestinal submucosa (SIS),[1,9,10] urinary bladder,[11-13] renal capsule,[27] pericardium,[8] tissue adhesives,[7] and conjunctiva/tarsoconjunctiva.[14-18] All the above provide different degrees of tectonic support to the eye but, unfortunately, not all of them would maintain corneal transparency, which is one of the most important factors for vision, especially when the

TABLE 1 Qualitative and quantitative variables (absolute and relative frequencies), age, and follow-up were described by median and their 95% confidence interval (95% CI) and absolute range (minimum and maximum)

			Corneal graft opacity		
		Total n = 100	(grade 0-2) n = 62	(grade 3-4) n = 38	*P*-value
Age (y)	Median (95% CI)	5 (5;7)	5 (5;8)	4 (3;6)	.335
	Range	0.3-17	0.6-17	0.3-15	
Breed	Brachycephalic	65%	39%	26%	.668
	Mesocephalic/Dolichocephalic	35%	23%	12%	
Defect					
Type	Full-thickness	51%	29%	22%	.309
	Deep stromal/Descemetocele	49%	33%	16%	
Location	Central	57%	35%	22%	1.000
	Paracentral	43%	27%	16%	
Graft					
Size	0-4 mm	84%	51%	33%	.589
	>4 mm	16%	11%	5%	
Direction	From dorsal	67%	41%	26%	1.000
	From ventral/lateral/medial	33%	21%	12%	
Suture material	Polyglactin 910	52%	34%	18%	.538
	Polyglycolic acid	48%	28%	20%	
Most common concurrent ocular diseases					
Euryblepharon	No	58%	41%	17%	*.040*
	Yes	42%	21%	21%	
Euryblepharon (surgically corrected)	No	34%	15%	19%	.238
	Yes	8%	6%	2%	
KCS	No	60%	40%	20%	.295
	Yes	40%	22%	18%	
Medial-Inferior entropion	No	68%	44%	24%	.509
	Yes	32%	18%	14%	
Pigmentary keratitis	No	87%	58%	29%	*.028*
	Yes	13%	4%	9%	
Calcic/Lipid corneal deposits	No	89%	55%	34%	1.000
	Yes	11%	7%	4%	
Distichiasis	No	91%	56%	35%	1.000
	Yes	9%	6%	3%	
Visual outcome	Positive	96%	61%	35%	.152
	Negative	4%	1%	3%	
Follow-up (d)	Mean	108.9	101.4	121.4	.225
	Standard deviation	143.7	151.3	131.2	

Note: Fisher's exact test was use for qualitative variables and Mann-Whitney U test for quantitative variables.
Statistically significant *P*-values are underlined and in italics.

defect is affecting the visual axis. Despite the good overall success reported in the aforementioned grafting techniques, variable degrees of corneal opacification and moderate to high rejection rates have been reported, which may need longer and more intensive postoperative treatment. Particularly, homologous and heterologous corneal grafting procedures in canine species have been related to a rejection rate up to 56%, requiring rescue medical treatment for its control and, in some cases, surgical rescue, which may imply prolonged postoperative treatment and poor cosmetic and visual outcomes.[4]

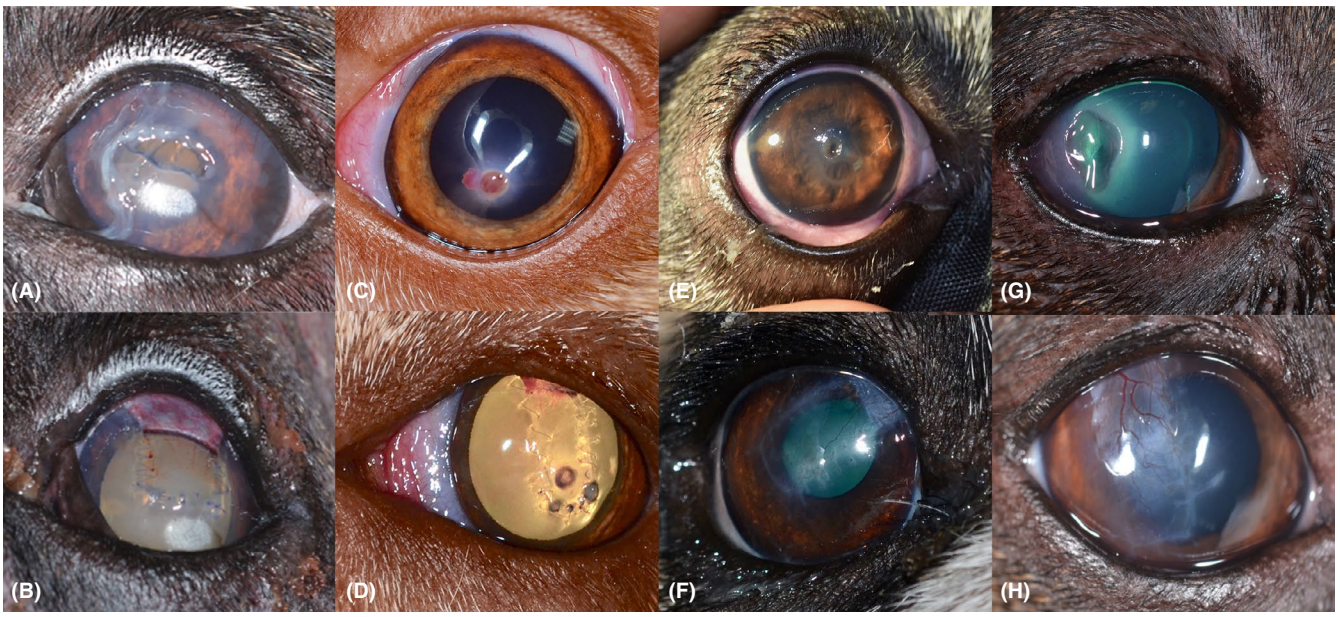

FIGURE 2 Pre- and postoperative outcome: (A) and (B) 5 y old German Shepherd male (2 wk re-check), (C) and (D) 4 y old medium cross-breed female (3 wk re-check), (D) and (E) 8 y old French bulldog male (14 mo re-check), (G) and (H) 7 y old Jack Russell Terrier male (12 mo re-check)

Conversely, graft rejection has not been described as frequently in cases of amniotic membrane, porcine small intestinal, or urinary bladder submucosa, as those tissues present a decreased susceptibility to bacterial colonization, potential to inhibit matrix metalloproteinases, and a low antigenic potential.[1,9,10,19-21] Nevertheless, other serious complications have been described with the use of those biomaterials, such as severe granuloma formation, graft pigmentation, graft failure, suture/graft dehiscence, phthisis bulbi, and keratoconus, which may also affect the transparency of the visual axis.[9,19] Besides Dorbandt et al study (2015) stating that conjunctival pedicle flap alone or with underlying acellular submucosa implant may maintain globe integrity in cases of deep corneal ulcer or perforation, with a success rate of 93%, it is generally accepted that conjunctival grafts in dogs induce moderate to high degrees of corneal opacification and are commonly discouraged in cases of large corneal perforations. Unfortunately, in Dorbandt´s study, the size of the corneal defects was not specified, no corneal clarity score was used and no evaluation of vision recorded.[18] Nevertheless, considering that the majority of defects in that study were located in the central cornea, one could hypothesize a high degree of opacification, and consequently visual impairment, mainly during the day. In addition, renal and SIS corneal grafting have been suggested as an effective method for corneal reconstruction and as an excellent alternative to conventional conjunctival grafts. However, marked cicatricial leukoma formation and pronounced corneal pigmentation have been reported in some of the cases, with consequent visual impairment.[1,27] Finally, some reports describe the use of tissue adhesives such as the cyanoacrylate glue to successfully manage corneal ulcers (superficial or stromal ulcers and descemetoceles), corneal lacerations, lamellar keratectomy, and small perforations.[7,28] Nevertheless, glue is not indicated to restore corneal integrity in deep or large corneal defects, nor in infected lesions as the glue plug could come off prematurely.[29,30]

Seeking a surgical technique that could provide adequate tectonic support, induce low axial corneal opacity and have a high availability, short postoperative period and low immune rejection risk, CCT was considered a promising technique to be evaluated. As previously mentioned, the surgical procedure described in the herein is a modification of the technique initially described by Parshall et al, in which a flap of cornea and sclera was advanced to cover the corneal defect.[22] The two main advantages of a CCT when compared with CST are less demanding surgical technique and better final paraxial corneal transparency (conjunctiva vs sclera). Both, CST and CCT, imply far less central or axial scaring compared with conjunctival or frozen corneal grafts.[30] Generally, a slight peripheral linear opacity remains from the transposed limbus, with varying degree of pigmentation, but the cornea tends to heal clearly over the center.[30] In feline patients, it has been observed that even the conjunctival part of the graft becomes transparent over time.[23,24] In the present study, some tendency for conjunctival transparency was also observed, but the exact mechanism behind this event remains unknown. Theories evaluated and verified in human medicine are that conjunctival epithelium can transdifferentiate into corneal epithelium,[31] and in patients with limbal defects, corneal epithelial cells may replace conjunctival epithelium.[32] In the dog, although the microanatomy and physiology of the limbus and stem cells is not deeply understood, limbal epithelial

stem cells seem to play a pivotal role in maintaining corneal epithelial health and thus, corneal clarity.[33] By moving the limbus to the central cornea, stem cells could help in increasing the transparency, not only of the axial corneal area, but also of the conjunctival graft.

As stated earlier, in other surgical procedures when frozen or synthetic grafts are used, corneal vascularization has been determined to be one of the most important risk factors for immunologic graft rejection, directly associated with the number of blood vessels per corneal quadrant.[34] Theoretically, this risk is not present with CCT as the grafted corneal and conjunctival tissues are autologous. Furthermore, conjunctival vessels and lymphatics offer significant antibacterial, antifungal, antiviral, antiprotease, and anticollagenase effects, thus leukocytes, antibodies, serum, and a2-macroglobulin are rapidly incorporated into the corneal ulcer bed, helping in the healing process.[35] What is more, because of the conjunctival blood vessels, systemic antibiotics, when used, can reach the ulcer site in higher levels.[35]

The present study suggests that CCT should be considered a valuable surgical technique for the treatment of small to medium deep stromal ulcers, descemetoceles, and corneal perforations in dogs. This study shows promising results in terms of globe and vision preservation (100% and 96%, respectively), but also in the maintenance of central corneal transparency (62% of the cases showing faint to mild degree of CGO). Although brachycephalic skull conformation has been postulated to predispose to corneal ulcerative disease,[4,18,36-38] brachycephaly was not a risk factor statistically significant for the degree of CGO post-CCT in the present study, obtaining similar outcome in terms of transparency for the brachycephalic and non-brachycephalic dogs ($P = .668$). Conversely, euryblepharon turned out to be directly related to postsurgical CGO ($P = .040$). This result is consistent with previous data showing that the presence of a large palpebral fissure and a shallow orbit may additionally play an interactive role in the pathogenesis of corneal ulcerative disease and may be considered a risk factor for corneal healing.[37] Indeed, those breeds have also been associated to have a reduced number of corneal nerve endings and thus a slower corneal healing.[39] Conversely to the use of other grafts that do not restore normal corneal innervation, it could be postulated that by performing a CCT, partial preservation of primary corneal innervation could be achieved, improving the healing process in this way. Further studies (histopathological, immunohistochemical labeling of corneal nerves and microscopical using advanced imaging techniques) would be needed to confirm this hypothesis. Surprisingly, those patients with euryblepharon that underwent concurrent canthoplasty at the time of the CCT showed similar CGOs levels than the ones in which the palpebral fissure was not surgically reduced ($P = .238$). These findings suggest a multifactorial etiology for the higher degree of postoperative CGOs seen in dogs with concurrent euryblepharon.

Pigmentary keratitis was another concurrent ocular disease statistically and directly associated with corneal transparency results ($P = .028$). Although pigment was initially not affecting the corneal graft, overgrowth and CCT invasion was seen postoperatively in almost all the affected cases. Surprisingly, KCS seemed to not affect corneal opacification in this study ($P = .295$). Nevertheless, the interpretation of these results should be undertaken with caution. Although severe and untreated cases of KCS may lead to progressive pigmentary keratitis, with extensive corneal vascularization, with or without ulceration,[40] many of the cases in the present study that had chronic KCS, were already under treatment with topical cyclosporine and artificial tears, which makes comparison between cases somehow unreliable. Furthermore, given that cyclosporine has been reported to inhibit corneal angiogenesis[41] and reduce corneal pigmentation in dogs,[42,43] one could hypothesize that it may also limit the progression of corneal pigmentation in the controlled KCS cases post-surgically.

Among some of the intrasurgical issues that could potentially affect the CGO in this study (size, depth, location and direction of the CCT, and choice of suture material), none of them seemed to be statistically associated with the CGO outcome ($P > .05$). In canine heterologous keratoplasties, the size of corneal donor button has been directly associated with poor surgical outcomes due to higher immune rejection rates.[4,5] In the present study, the size of the corneal advanced flap did not influence CGO or visual outcome, which, in part, could be due to the lack of immunologic rejection to the autologous corneoconjunctival tissue. This last feature is especially important in canine patients, as many cases are usually presented with severe degrees of corneal inflammation that could potentially increase the rejection rate. Surprisingly, the depth of the defect was not related to the degree of CGO, with statistically similar results for corneal perforation and descemetocele/deep stromal ulcers. Although corneal endothelial cell mitosis has not been described in adult dogs, the small diameter of corneal perforations in this study could mean that lost endothelium could have been potentially restored by enlargement and migration of the surrounding endothelial cells.[44] Further specular microscopy studies are needed to confirm this hypothesis.

When possible, the selected graft direction was dorsal (67%), although in cases in which this could not be achieved, other directions were used. Various reasons justify this surgical approach as it permits a more anatomically comfortable position for the surgeon for tissue manipulation and suturing, also avoiding interposition of the nictitating membrane ventrally. What is more, dorsal direction bypasses the effect of eyelid perpendicular movement on graft stability, compared

with nasal or temporal direction. Nevertheless, another important point to consider regarding graft direction is the choice of the side closest to the limbus, aiming to damage the least amount of healthy corneal tissue as possible. Either way, the surgeon must always confirm that enough healthy corneal tissue is available to cover the defect without tension. It is important to point out that 84% of the treated defects in the present study were smaller than 4 mm in diameter, so the availability of enough healthy corneal tissue is indispensable for this surgical technique. In the present study, graft direction did not affect in a statistically significant manner the CGO outcome.

Although monofilament nonabsorbable sutures are less reactive for the cornea and are directed at reducing the accumulation of host inflammatory cells into the graft,[35,45] in the present study, absorbable suture was applied in all cases in order to avoid the need for a second anesthesia to remove suture material and bearing in mind that autologous graft should generate less inflammatory response. No differences in terms of CGO were neither observed between 9-0 polyglycolic acid and polyglactin 910 ($P = .538$).

To the authors´ experience and in concordance with the intrasurgical complications seen in the present study (7%), the most delicate surgical steps to be considered are as follows: the size and depth of the graft, the lack of graft tension, the harvesting of the limbus and conjunctiva, and last, but not least, the appropriate preparation of the tissue bed. Those steps are even more difficult in perforated eyes, in which despite the use of viscoelastic, the preparation and suture of the graft can be challenging. Among those steps, perhaps the most delicate one is the dissection of the corneoconjunctival limbus union, as too superficial dissection may create holes in the graft. It too should be emphasized that technical comparison to other surgical techniques is rendered difficult as few articles report intrasurgical complications in detail.

Postoperative complications were detected in relatively low number of cases (21%) and were mild, with only three major complications requiring rescue surgery, but all eyes remained visual at last re-check. This percentage is either similar or lower than the previously reported for other techniques used in the treatment of similar corneal diseases.[1,3,4,7,8,18,20] In comparison with the use of CCT in feline patients,[23,24] more postoperative complications were detected in the present study. Nevertheless, the underlying disease may have influenced those outcomes as all cats were treated for corneal sequestra. Although it is difficult to compare results between different studies, this relevant interspecies difference has already been reported in mixed studies,[1,8-10] suggesting inequal corneal healing among species.

The present study has the limitations of a retrospective multicentric study. Surgeries were performed by various surgeons, and consequently variable postoperative treatments were established. In addition, the follow-up time was affected by different referral protocol according to the country where the surgery was performed. To avoid subjective evaluations by each surgeon, data collection was standardized, and presurgical and last follow-up pictures were provided for most of the clinical cases included in the study and objectively re-evaluated by one person. Ideally, future prospective studies would be necessary for the evaluation of CGO of corneal surgical techniques and concretely CCT. Nowadays, there is an available and certified corneal clarity score that reached substantial to almost perfect inter- and intra-observer reproducibility and reliability and will be surely more precise in comparing outcomes of surgical techniques between authors and surgeons in future studies.[46] However, given the retrospective nature of this study, the authors chose an opacification grading system previously established by some of the co-authors (ML and TP) and repeatedly used in various major retrospective studies on corneal surgery in veterinary medicine.[4,20,26] Finally, despite being the first published study on CCT in dogs, the relatively low number of cases remains a limitation and may preclude further conclusive statistics on the influence of different variables. Nevertheless, the authors consider the present study to be a representative sample of everyday practice, providing a highly useful and accurate new data.

In conclusion, CCT is an effective surgical treatment for small to medium deep stromal ulcers, descemetoceles, and full-thickness corneal defects in dogs, achieving a highly satisfactory corneal graft transparency and visual outcome.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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