Technical Feasibility of Whole-eye Vascular Composite Allotransplantation: A Systematic Review

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Background: There are over 43 million individuals in the world who are blind. As retinal ganglion cells are incapable of regeneration, treatment modalities for this condition are limited. Since first incepted in 1885, whole-eye transplantation (WET) has been proposed as the ultimate cure for blindness. As the field evolves, different aspects of the surgery have been individually explored, including allograft viability, retinal survival, and optic nerve regeneration. Due to the paucity in the WET literature, we aimed to systematically review proposed WET surgical techniques to assess surgical feasibility. Additionally, we hope to identify barriers to future clinical application and potential ethical concerns that could be raised with surgery.

Methods: We conducted a systematic review of PubMed, Embase, Cochrane Library, and Scopus from inception to June 10, 2022, to identify articles pertaining to WET. Data collection included model organisms studied, surgical techniques utilized, and postoperative functional outcomes.

Results: Our results yielded 33 articles, including 14 mammalian and 19 cold-blooded models. In studies performing microvascular anastomosis in mammals, 96% of allografts survived after surgery. With nervous coaptation, 82.9% of retinas had positive electroretinogram signals after surgery, indicating functional retinal cells after transplantation. Results on optic nerve function were inconclusive. Ocular-motor functionality was rarely addressed.

Conclusions: Regarding allograft survival, WET appears feasible with no complications to the recipient recorded in previous literature. Functional restoration is potentially achievable with a demonstrated positive retinal survival in live models. Nevertheless, the potential of optic nerve regeneration remains undetermined. *(Plast Reconstr Surg Glob Open 2023; 11:e4946; doi: 10.1097/GOX.0000000000004946; Published online 25 April 2023.)*

INTRODUCTION

Approximately 40 million individuals in the world are blind, and with this comes a demand for vision restoration.[1] In 1885, Bradford performed the first documented whole-eye transplantation (WET), specifically, a xenotransplant of an enucleated eye from a rabbit to a human.[2] Dr. Bradford's report outlines how the optic nerves (ONs) of the host and recipient were coapted and documents postoperative "ocular movements in all directions."[2] However, the lack of vascular anastomosis and immunosuppressive therapy inevitably led to allotransplant failure.

After this initial attempt, interest in WET grew, and multiple scientists successfully performed WET in animal models. In several of these cases, the ocular allograft not only survived but restored vision as well.[3–5] With this, WET was again pursued on a human in 1969.[6] However, after the failure of this attempt, the medical community condemned the operation and the National Eye Institute advised against further investigations into the procedure.[7] The report claimed that mammalian ocular reperfusion, intrinsic characteristics of the mammalian ON, and allograft rejection were insurmountable barriers to successful WET.[7]

Although efforts to restore ocular function in humans by retinal transplantation have been ongoing, vision restoration has remained out of reach. Meanwhile, new microsurgical techniques, immunomodulation protocols, and

Disclosure statements are at the end of this article, following the correspondence information.

neuroregenerative therapies have circumvented previously existing barriers to vascular composite allotransplantation (VCA). In fact, since the first accomplished hand transplant in 1998, over 200 successful VCAs have been performed.[8] These advances in VCA technologies have led to the re-emergence of primary literature on WET. Although vision restoration remains the ultimate goal, WET may also be warranted in the case of eye enucleation after facial trauma, especially when facial transplantation is already planned.

This study aimed to systematically review all available literature on WET and compiled the research methodology employed, proposed surgical techniques, and documented allograft outcomes in order to evaluate surgical feasibility. Furthermore, we identified gaps in the literature and potential barriers to future clinical practice. Finally, we raised ethical considerations that may be associated with WET in live human recipients.

METHODS

A systematic review was conducted after the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 guidelines using MEDLINE, PubMed, Cochrane, and Scopus databases with no restriction on time of publication. Search terms related to ocular transplantation were used. A complete list of search terms is presented in Table 1. Studies were uploaded to Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) software to optimize screening and reduce bias. Title and abstract screening, as well as full-text screens, were conducted by two independent reviewers (M.L., N.D.). Conflicts were resolved by a third party (B.F.C.). Due to the paucity of literature on the topic, relevant abstracts where no full text was available were included for discussion.

Inclusion and exclusion criteria are outlined in Table 2. Data extraction and tabulation were performed independently by two reviewers (M.L., N.D.). Data

Takeaways

Question: Is a whole-eye transplant (WET) currently feasible?

Findings: With prospects of transition to human attempts, this work systematically reviews the available literature on WET to assess its technical feasibility from allograft survival and ocular functionality standpoints. The findings illustrate that in cold-blooded species, WET is possible with organisms resuming vision and ocular movement after transplant. In mammalians, while allograft integrity and retinal survival were verified after surgery, optic nerve regeneration is yet to be determined.

Meaning: Transition to human attempts of WET may occur if performed according to current ethical standards.

extraction included study year of publication, model organism employed, surgical techniques (anastomotic connections, allograft components), and operative outcomes (allograft viability, oculomotor function, vision restoration). When any of the aforementioned items were not explicitly addressed in the article, it was marked as not reported.

RESULTS

Our search yielded a total of 2961 articles. After title and abstract screening, 61 articles transitioned to full-text screening. Thirty-three articles were ultimately included (Fig. 1). Some studies mentioned clinical aspects of WET from previously published results on mammalian organisms.[9,10] Because these did not provide novel data for assessment, they were excluded. Fourteen articles utilized mammalian and cadaveric models.[2,11–23] The remaining 19 utilized cold-blooded species.[3–5,24–39] After data extraction, a total of 1998 eyes were included, 1831 of which belonged to nonmammalian organisms and 167 to mammals, including 13 human cadavers and two living humans.

In cold-blooded model organisms, the surgical procedures included enucleation of the recipient eye and insertion of the transplanted allograft into the host orbit. No surgical coaptation between donor and recipient ON was carried. Vascular anastomosis was not explicitly addressed in these articles. Further surgical techniques employed in cold-blooded model organisms are present in Table 3. Regarding ocular function, in approximately 18% of cold-blooded organisms, vision restoration was achieved. Further results on nonmammalian organisms are summarized in Table 4.

For mammalian models, surgical techniques and allograft composition are indicated in Table 5. Regarding nerve coaptation, all studies but one performed coaptation between central nervous system (CNS) nerves. Zor et al utilized a murine model and elected to coapt the donor ON with the recipient's greater auricular nerve, a peripheral system nerve.[19] Davidson et al and Sher et al also included the oculomotor nerve (CN III) in their donor cadaveric and rodent allograft.[15,23] While previous studies

Table 1. Search Term Criteria

Search Terms	PubMed/MEDLINE
	Whole-eye transplant* [tw]
	Eye transplant* [tw]
	Ocular transplant* [tw]
	Eye allotransplantation [tw]
	Ocular allotransplantation [tw]
	Eye vascularized composite allotransplantation [tw]
	Ocular vascularized composite allotransplantation [tw]
	Eye vascularized composite allograft [tw]
	Ocular vascularized composite allograft [tw]
	Eye allograft [tw]
	Ocular allograft [tw]
	Eye composite tissue allotransplantation [tw]
	Ocular composite tissue allotransplantation [tw]
	Eye composite tissue allograft [tw]
	Ocular composite tissue allograft [tw]

Table 2. Study Selection Criteria

	Inclusion Criteria	Exclusion Criteria
Article type	Any article reporting surgical techniques involved in whole-eye transplantation performed in models	Any article that did not address WET in model organisms
Surgical procedure conducted	Whole-eye transplantation or any procedure focused on advancing WET methods	Retinal-only, cornea-only surgeries
Model organism studied	Living or cadaveric mammals, reptiles, or fish	Embryos or insects
Language		Non-English papers
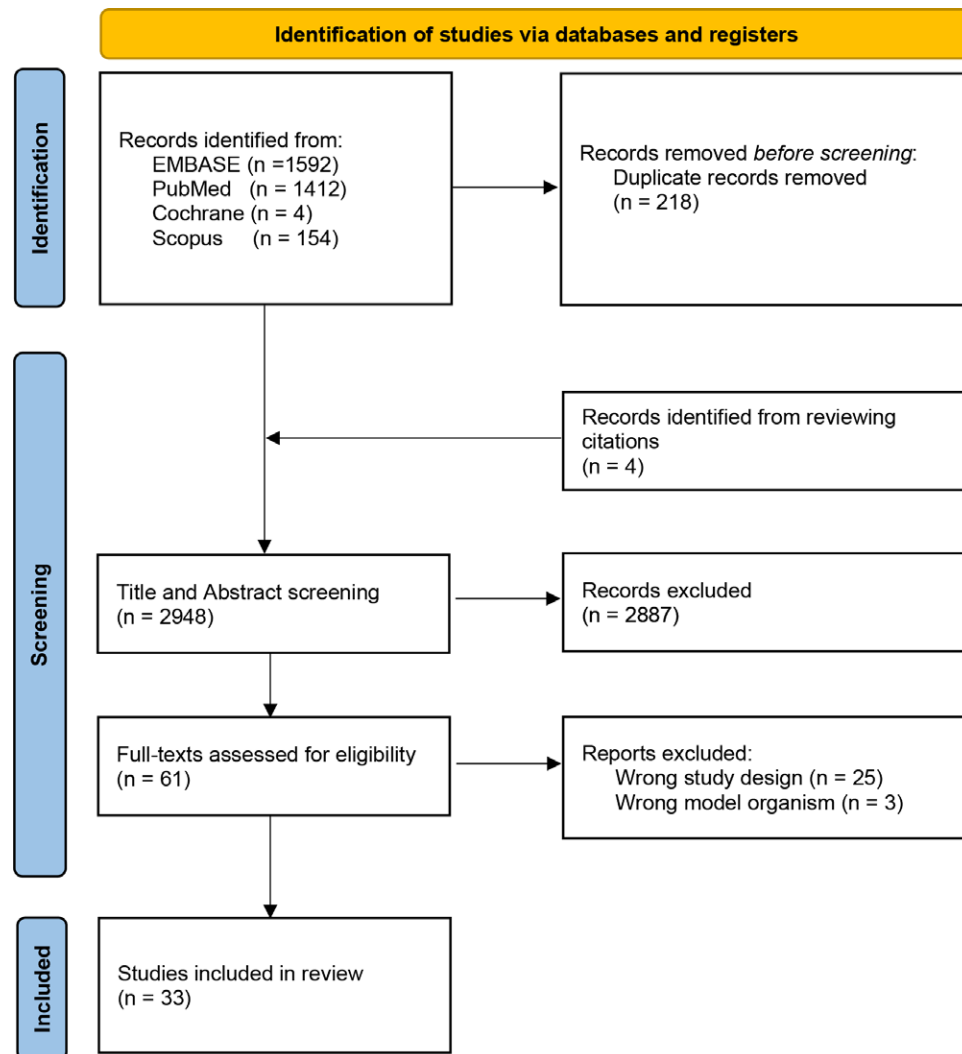
Fig. 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow chart.

performed WET alone, recent studies have included soft tissue and skeletal components associated with the donor eye allograft, including the bony orbit, the frontal bone, eyelids, and ears.[18–20,22,23] All arterial anastomoses were made end-to-end except for Davidson et al, who utilized human cadaveric vein grafts for arterial anastomotic connections between the vessels of the allograft and recipient.[9] The surgical outcomes in mammalian models are presented in Table 6.

Regarding ocular functional restoration after surgery, three articles carried out studies examining retinal survival after transplantation via electroretinogram (ERG) testing. In these, 35 organisms were examined and 29 had positive ERG results, suggesting retinal ganglion cell survival after WET. In addition, three mammalian studies reported ocular movement testing.[2,11,12]

Due to the novelty of the surgery, only a few articles included histologic analysis (Table 7). Common findings include the presence of macrophages, inflammatory cells, and signs of necrosis in transplanted retinal ganglion cells (RGCs) after graft loss.[14,19,40–42] Notably, one study found that perfusion of the postprocurement allograft

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Table 3. Ectotherm Model Organisms: Surgical Techniques

First Author (Year of Publication)	Model Organism	Number of Eyes in Experiment	Structures Included in Graft
Keeler (1929)[24]	Frog	60	Eye
Stone (1930)[27]	Salamander	82	Eye, CN II
Stone (1937)[30]	Salamander	126	Eye, CN II
Schwind (1937)[30]	Frog	247	Eye
Stone (1938)[26]	Salamander	Over 700	Eye
Stone (1940)[29]	Salamander	59	Eye
Weiss (1942)[32]	Lizard	45	Eye, CN II
Stone (1943)[28]	Salamander	26	Eye, CN II
Sperry (1945)[33]	Frog	51	Eye, CN II
Stone (1945)[4]	Salamander	80	Eye
Stone (1946)[5]	Salamander	70	Eye
Sperry (1949)[34]	Fish	22	Eye, CN II
Bytinski-Salz (1956)[35]	Fish	60	Eye, CN II
Heath (1957)[36]	Salamander	14	Eye
Stone (July 1964)[25]	Salamander	11	Eye
Stone (December 1964)[25]	Salamander	26	Eye
Schneider (1968)[37]	Salamander	24	Eye
Pietsch (1985)[38]	Salamander	25	Eye, CN II
Pietsch (1988)[39]	Salamander	88	Eye, CN II, periorbital skin

with preservative solution before donor placement, and anastomosis resulted in decreased expression of phospho-c-Jun (PNJ+), an apoptotic marker.[43] In addition to histologic outcomes, the viability of ocular chambers was assessed, and intraocular pressures between the WET and native eye were found comparable.[40]

DISCUSSION

With previous studies in the literature demonstrating successful revascularization of the allograft posttransplantation and positive retinal ERG response upon stimulation, WET seems to be a viable option in cold-blooded and mammalian species, though oculomotor function remains poorly studied.

Anatomic and Vascular Considerations

The principal concern regarding tissue viability is appropriate perfusion of the ocular allograft after transplantation. Before the advent of microsurgery, vascular anastomoses were not established properly in WET models.[44] The lack of microsurgical techniques likely contributed to the poor survival rate of eyes presented in early studies of WET in mammals.[2,11–13] After Sher et al performed the first vascular anastomosis within the context of ocular transplantation in mammals,[16] all future WET allografts remained viable in the immediate posttransplantation period.[15,17,21,22] Likewise, while initial instances of WET occurred in heterotopic sites, later transplantation of the eye to orthotopic sites resulted in success.

Over time, surgeons have explored the feasibility of larger and more comprehensive eye allografts to include periorbital soft tissue and bones.[18,20] While transplantation of surrounding tissue could theoretically pose a threat to the viability of the eye by limiting space for postoperative edema, if successful, this may serve as a proof of concept for WET to occur concomitantly with FT in the future.[19,22] Moreover, in unilateral ocular and periorbital tissue transplantation, authors did not identify any adverse structural or functional effects in the native, contralateral eye, contrary to commonly reported sympathetic ophthalmia after eye trauma.[45] In summary, our results suggest that ocular allograft perfusion and survival are likely with current technological and surgical advancements.

Going forward, surgical techniques developed in rodent and porcine models may be translated to further human cadaveric studies. Of note, some human arteries may be shorter in length. Thus, the appropriate choice of arterial anastomosis ought to guide future practice. In the study by Davidson et al, surgeons explored different possible anastomotic connections, namely connecting the donor allograft ophthalmic artery to either the recipient's superficial temporal, facial, or internal maxillary artery. The facial and internal maxillary arteries were the closest match in diameter size to the donor's ophthalmic artery. Yet, they both required long venous grafts with the largest graft used being the facial artery. The internal maxillary artery required the smallest graft and was appropriately size-matched. However, it had no accompanying usable veins for anastomosis and thus was discarded as a possibility.[9]

Finally, Siemionow et al suggested that if periorbital tissue is included in the allograft, additional arterial anastomoses should be made to vascularly support added structures.[18] These include the ophthalmic artery to support the WET allograft and facial and superficial artery to support the additional bone and soft tissues (all six extraocular muscles, the surrounding bony orbit, and overlying skin). Thus, further anatomical cadaveric studies in humans are needed to establish a proper surgical technique dependent upon the size of the allograft created.

Ocular Functionality and the Nervous System

After allograft viability, one hope with WET is the restoration of ocular function, which includes both movement

Table 4. Ectotherm Model Organisms: Surgical Outcomes

First Author (Year of Publication)	Number of Eyes Viable after Surgery	Perfusion Recorded	Ocular Movement	Nervous Test	Type of Elicit Response	Responses Recorded	Vision Return
Keeler (1930)[24]	23	Yes	No	Yes	Light-pupillary response	17/17 (100%)	0/23 (0%)
Stone (1930)[27]	74	Yes	33	Yes	Light-pupillary response	6/6 (100%)	6/6 (100%)
Stone (1937)[30]	52	Yes	52	Yes	Light-pupillary response	52/52 (100%)	25/26 (96.2%)
Schwind (1937)[30]	95	No	"The majority"	No	N/A	N/A	0/95 (0%)
Stone (1938)[26]	N/R	Yes	"Most"	Yes	Light-pupillary response	"Many"	80/700 (11.4%)
Stone (1940)[29]	48	Yes	48	Yes	Light-pupillary response	6/6 (100%)	0% (0/4)
Weiss (1942)[32]	40	No	No	Yes	Baro-response (eyelid-closure)	38/40 (95%)	NR
Stone (1943)[28]	15	Yes	"Many"	Yes	Light-pupillary response	13/26 (50%)	4/26 (15.4%)
Sperry (1945)[33]	22 (12 adults, 10 tadpoles)	No	14 (2 tadpoles, 1 2 adults)	Yes	Object recognition (optokinetic move)	2/30 (tadpoles) 8/16 (adults)	2/30 (tadpoles) 12/16 (adults)
Stone (1945)[4]	33	No	"Most eyes"	Yes	Light-pupillary response	33/33 (100%)	8/33 (24.2%)
Stone (1946)[5]	12	Yes	12	Yes	Light-pupillary response	12/56 (17.65%)	12/56 (17.65%)
Sperry (1949)[34]	22	Yes	"Several"	Yes	Object recognition (optokinetic move)	7/16 (43.75%)	7/16 (43.75%)
Bytinski-Salz (1956)[35]	19	No	No	No	N/A	N/A	No
Heath (1957)[36]	14	Yes	No	No	N/A	N/A	N/R
Stone (July 1964)[25]	10	Yes	No	Yes	Light-pupillary response	7/10 (70%)	7/10 (70%)
Stone (December 1964)[25]	17	Yes	No	Yes	Light-pupillary response	9/17 (52.9%)	9/17 (52.9%)
Schneider (1968)[37]	21	No	19	Yes	Light	21/21 (100%)	21/21 (100%)
Pietsch (1985)[38]	19	No	No	Yes	Melanophore changes	19/25 (76%)	N/R
Pietsch (1988)[39]	88	Yes	No	Yes	Melanophore changes	18/22 (heterograft) 17/22 (autograft)	N/R

N/A, not applicable; N/R, not recorded.

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Table 5. Mammalian Model Organisms: Surgical Techniques

First Author (Year of Publication)	Model Organism	Allograft Structures	Number of Eyes Studied	Transplant Location	Nerves Coopted	Donor Vessels	Recipient Vessels
Bradford (1885)[2]	Human (living)/rabbit	Eye, CN II	1	Eye orbit	CN II	N/R	N/R
May (1886)[11]	Rabbit	Eye, CN II	24	Eye orbit	CN II	N/R	N/R
Koppanyi (1925)[12]	Mouse	Eye	25	Eye orbit	CN II	N/R	N/R
Burns (1971)[13]	Human (living)	Eye, CN II, lateral rectus muscle	1	Eye orbit	N/A	Anterior ciliary artery	Anterior ciliary artery
Freed (1980)[14]	Mouse	Eye	12	Leg	N/A	N/R	N/R
Sher (1980)[16]	Rat/dog	Eye	25	Cortical brain	N/A	Ophthalmic artery (dog)	Femoral artery (rat)
Sher (1981)[15]	Sheep	Eye, CN II, recti and oblique muscles	20	Eye orbit	CN II, III	1) Ciliary artery 2) Internal ophthalmic arteries	1) Ciliary artery 2) Internal ophthalmic arteries
Shi (2009)[17]	Pig	Eye, CN II	20	Neck	N/A	Ophthalmic artery	Carotid artery
Davidson (2016)[23]	Human (cadaver)	Eye, recti and oblique muscles, CN II, III, IV, VI	8	Eye orbit	CN II, III, IV, VI	Ophthalmic artery	Superficial temporal or Internal maxillary artery
Siemionow (2018)[18]	Human (cadaver)	Eye, recti and oblique muscles, bony orbit4, skin, CN II, CN III	5	N/A	CN II, III	1) Facial artery and superficial temporal artery 2) Ophthalmic artery	N/R
Zor (2019)[19]	Mouse	Eye, recti and oblique muscles, CN II, earlobe	5	Neck	CN II (donor) greater auricular nerve (recipient)	Common carotid artery	Common carotid Artery
Bravo (2020)[20]	Pig (cadaver)	1) Eye, bony orbit, earlobe 2) Eye, bony orbit 3) Eyes, bilateral bony orbit, frontal bone, ears	8	N/A	N/A	External carotid artery	External carotid artery (theoretical)
Badaro (2022)[21]	Rabbit	Eye, CN II	6	Eye orbit	CN II	N/A	N/A
Komatsu (2022)[22]	Mouse	Eye, bony orbit, eyelid, auricle, CN II	7	Eye orbit	CN II	Carotid artery	Carotid artery

N/A, not applicable; N/R: not recorded.

Table 6. Mammalian Model Organisms: Surgical Outcomes

First Author (Year of Publication)	Number of Eyes Viable after Surgery	Perfusion Recorded	Ocular Movement Recorded	Optic Function Test	Type of Test	Responses Recorded
Bradford (1885)[2]	0/1 (0%)	Yes	Yes (maintained for indetermined time)	No	N/A	N/A
May (1886)[11]	4/24 (16.7%)	Yes	Yes (4/24)	Yes	Object recognition	0/24 (0%)
Koppanyi (1925)[12]	5/25 (20%)	Yes	Yes (3/25)	Yes	Light reaction (pupillary response)	1/25 (4%)
Burns (1971)[13]	0/1 (0%)	Yes	Yes (before graft loss)	No	N/A	N/A
Freed (1980)[14]	10/12 (83.3%)	Yes	No	Yes	Light reaction (ERG activity)	3/9 (33.3%)
Sher (1980)[16]	25/25 (100%)	Yes	No	No	N/A	N/A
Sher (1981)[15]	20/20 (100%)	Yes	No	No	N/A	N/A
Shi (2009)[17]	20/20 (100%)	Yes	No	Yes	Light reaction (ERG activity)	20/20 (100%)
Davidson (2016)[23]	N/A	No	N/A	No	N/A	N/A
Siemionow (2018)[18]	N/A	Yes (ex vivo)	N/A	No	N/A	N/A
Zor (2019)[19]	5/5 (100%)	Yes	No	No	N/A	N/A
Bravo (2020)[20]	N/A	Yes (ex vivo)	No	No	N/A	N/A
Badaro (2022)[21]	6/6 (100%)	N/A	No	Yes	Light reaction (ERG activity)	6/6 (100%)
Komatsu (2022)[22]	7/7 (100%)	Yes	No	Yes	MRI/ion transport along optic tract	0/7 (0%)

N/A, not applicable.

Table 7. Histological Examination of WET Graft

First Author (Year of Publication)	Immuno-modulator Added	Dose	Histological/Biochemical Analysis
Freed (1980)[14]	None	N/A	• Graft necrosis • Ocular tissue disorganization
Chen (2018)[40]*	Tacrolimus	1 mg/kg/d	• Ocular chronic inflammation • Retinal degeneration • No on degeneration
Chen (2018)[41]*	Tacrolimus	1 mg/kg/d	• Ocular chronic inflammation • Retinal degeneration • No graft necrosis
Zor (2019)[19]	Cyclosporine A	16 mg/kg/d [POD 0]–2 mg/kg/d [POD 21]	• Graft necrosis • On macrophage infiltration • Retinal degeneration
Su (2022)[42]*	None	N/A	• Lymphocytic infiltration • Corneal rejection • Ocular tissue disorganization
Khatter (2022)[43]*	Wisconsin solution BaCl2 Valproic acid	N/R	• Decrease PNJ+ expression

*Abstract only.
N/A, not applicable; N/R, not recorded.

and vision. To achieve this, ON coaptation must occur between the donor tissue and recipient orbit. RGCs must also survive transplantation.[46] In cold-blooded species, the RGCs and ON have innate regenerative properties owing to their strong growth-stimulating capacities and intrinsic retinal astrocyte growth-inducing factors.[47] In these species, researchers opted to merely approximate donor and recipient ONs,[2–4,26–36] and vision restoration was found in over 50% of transplanted organisms.[2,27,28,37–40] This is in stark contrast with mammalian models, which have yet to report vision perception after WET, even when a retinal response to light was detected and eye perfusion was maintained.[9]

Studies using ERG on mammalian organisms have demonstrated that retinal response to light exponentially decreases as the time from death increases.[48] However, mammalian ocular functionality was maintained when constant ocular perfusion occurred post-enucleation.[49,50] In studies where eyes were enucleated and artificially perfused, authors detected ERG signals hours after enucleation, indicating potential viability of donor retina.[49,50] Beyond successful preservation of harvested allograft tissue, retinal function after WET with ON coaptation was demonstrated in 29 of 35 transplanted mammalian eyes with positive ERG results.[12,14,17,21]

Bridging mammalian models to humans, Abbas et al utilized eyes of recently deceased individuals and concluded that hypoxia and acidification were the major factors impacting retinal viability.[48] The study found that the retina had the potential to remain viable for up to 20

minutes postmortem, supporting the potential for whole-eye donation in humans. In addition, brain dead patients had ERG-positive retinas upon examination, implying that even when the patient is considered brain dead, their ocular tissue and RGCs may remain functional.[51] Thus, brain dead patients may contribute to a donor pool for WET in humans.

In addition to the restoration of peripheral light sensation via retinal function, vision requires central interpretation. Therefore, the connection between RGCs and the optic cortex is paramount. Current literature proposes that, after ON injury, the optic tract integration between RGCs and the CNS is compromised.[52] In vivo MRI studies of murine WET found that anterograde transport remained possible after intravitreal ion injection, but retrograde transport halted at the coaptation site.[22] Hence, coaptation was incapable of functionally connecting the RGCs to the recipient's CNS. These findings align with the current literature indicating that the CNS is less likely to regenerate even with proper nervous coaptation.[10]

To overcome this inherent regenerative incapacity, researchers have employed peripheral nerve grafting to introduce Schwann and other support cells capable of inducing nerve regeneration. Studies following ON injury found regeneration improved upon coaptation across peripheral nerve grafts.[53] Similarly, peripheral nerve explants grafted into the vitreous body of the rodent eye promoted RGC survival in resected ONs.[54] Although studies collected in our review discuss the potential use of peripheral nerve grafting in WET,[22] this has yet to be implemented in vivo.

Immunomodulation in WET

After successful transplantation, acute rejection remains the main clinical challenge. Post-WET histological examination reported lymphocytic infiltration, corneal rejection, ocular tissue disorganization, and graft necrosis.[14,42] To mitigate such processes, our preliminary results indicate two main immunomodulators currently under investigation in the WET literature: tacrolimus[40] and cyclosporine A.[19]

Tacrolimus remains a mainstay immunosuppressive in VCA and solid organ transplantation.[55] It suppresses T-lymphocyte transduction and IL-2 transcription, both of which are involved in HLA-mediated rejection. Studies utilizing tacrolimus found limited histologic evidence of necrosis and chronic ocular inflammation after WET. Considering its role in expediting peripheral nerve regeneration, tacrolimus has been shown to exhibit a protective effect after ON damage and may even promote CNS regeneration.[56] Furthermore, the neuroprotective effects of tacrolimus seem to co-occur with its primary immunomodulatory function.[40] Alternatively, studies of WET utilizing cyclosporine A demonstrated wide tissue necrosis histologically. Therefore, the current literature suggests the increased strength of tacrolimus in both mitigating allograft necrosis and promoting ON health postsurgery.[40] Although ON regeneration remains an active area of research, and strategies to mitigate nervous tissue dysfunction are still lacking, interventions such as neuroprotective

medication may facilitate potential ON regeneration and contribute toward future vision restoration in vivo.

Beyond surgical technique and immunologic management, tissue preservation protocols broadly utilized in solid organ transplantation demonstrate promise in WET. In vivo murine studies found decreased PNJ+ expression in RGCs of allografts treated with Wisconsin solution, $BaCl_2$, and Valproic acid.[43] Treatment occurs via perfusion of the allograft after procurement and before inset. Because PNJ+ is a signal for tissue apoptosis, a decrease in PNJ+ RCGs signifies a reduction in retinal tissue death. Although the data discussed above are promising, immunosuppressive therapy continues to be a significant risk factor after transplantation, and rejection remains nearly ubiquitous.

Aesthetic and Psychosocial Benefits of WET

Other benefits of WET include improved aesthetics and psychosocial health in recipients. For blind patients, current standards of care are limited, with the majority of ocular prosthesis made of polymethyl methacrylate material.[57] In studies on the psychosocial dynamics of ocular prosthetic use, patients reported experiencing some degree of depression, anxiety, and stress as a result of people noticing their eye prosthesis.[58] On the other hand, with a biologic eye, the recipients may feel more comfortable in social settings. Social integration after face transplant is almost ubiquitous.[8] Because a biologic eye is expected to give a more natural feel when compared with currently available prostheses, it could be theorized that the patient would experience similar improvements in mental health, body image, and social integration. As such, we encourage a thorough appreciation of the psychosocial dimensions if WET is attempted again in humans.

Future Directions

Current and future research efforts are directed toward the eventual application of WET techniques in living human recipients. The studies reviewed herein provide foundational evidence to guide future research and identify areas in which further inquiry is needed. Although this review focuses on WET, the authors acknowledge that there are other areas of research with promising results in vision restoration, such as chips or three-dimensional bioprinting.[59,60] Thus, given the potential synergism between ophthalmologic biotechnology and VCA, future research may focus on utilizing WET as a scaffolding to drive vision restoration in patients without ocular globes due to trauma.

Beyond the surgical, neurological, and immunosuppression considerations reviewed in this article, initiating WET in living human recipients raises several key ethical considerations that should be addressed. These include:

- patients' perceptions of and desire for (1) nonvision-restoring WET and (2) vision-restoring WET, including aesthetic and functional considerations;

- risks and benefits of WET when compared with prosthetic alternatives;
- addressing any additive immunosuppressive risk for combined WET and facial transplantation when compared with facial transplantation alone;
- establishing a plan for managing potential allograft failure;
- psychosocial considerations for potential WET recipients and their loved ones, including concerns about personal identity related to the donor's eyes;
- public perceptions of whole-eye donation for WET and potential impact on solid organ and VCA donation;
- implications for corneal transplantation, if the donor would be eligible;
- consent for whole-eye donation;
- creation of mechanisms for ethical and equitable systemic allocation, distribution, and implantation of WET.

Although a detailed examination of these considerations is beyond the scope of the present article, we aim to identify important areas for future exploration and stimulate dialogue within the field to ensure that WET research proceeds responsibly, ethically, and with potential WET recipients' values and treatment goals at the center of inquiry.

Strengths and Limitations

With the field of WET still in its infancy, only a few studies have been published on the topic since the first VCA took place in 1998. Thus, we elected to include abstracts that pertained to the topic in our discussion. Further, owing to this paucity of data, our understanding of WET is only informed by a few quintessential studies, which are not without limitations.

Firstly, amphibian regeneration occurs on a pathway different than that of mammalian, thus precluding a direct application of those results to clinical practice. Secondly, some authors only harvested the allograft and then proposed possible vascular anastomotic connections from a theoretical perspective. Although beneficial to the propulsion of the field, the lack of studies with applications of these proposed allografts in humans renders many of the surgical techniques described in the literature inapplicable. Besides, of all the studied organisms, the maximum duration of follow-up was 3 weeks. After this period, MRI studies were carried out and indicated that ON regeneration did not take place. However, these results are met with reservations, considering nerve regeneration is very slow and may take months to show clinically detectable signs. Thus, assessments regarding ON regeneration remain largely inconclusive and warrant further investigation.

Even with these limitations, to our knowledge, the present study is the most updated compendium of WET studies. We hope the summation of these results will further the field of WET and potentially support a future human surgery.

CONCLUSIONS

Our results suggest that WET is technically feasible, and retinal response may be detected posttransplantation.

Recent studies have discussed the potential for ON regeneration in anticipation of WET attempts in the future. Although vision restoration has yet to be accomplished in mammalian WET, ocular transplants may be a feasible option to restore form in patients with enucleated orbits undergoing concomitant facial transplantation.

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DISCLOSURE

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