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Anesthetic Considerations in Facial Transplantation: Experience at NYU Langone Health and Systematic Review

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Background: Anesthetic considerations are integral to the success of facial transplantation (FT), yet limited evidence exists to guide quality improvement. This study presents an institutional anesthesia protocol, defines reported anesthetic considerations, and provides a comprehensive update to inform future directions of the field.

Methods: An institutional "FT Anesthesia Protocol" was developed and applied to 2 face transplants. A systematic review of 3 databases captured FTs in the peer-reviewed literature up to February 2020. Two reviewers independently screened titles and abstracts to include all clinical articles with FT recipient and/or donor-specific preoperative, intraoperative, and relevant postoperative anesthetic variables. Data charting guided a narrative synthesis, and quantitative synthesis reported variables as median (range).

Results: Our institutional experience emphasizes the importance of on-site rehearsals, anticipation of patient-specific anesthetic and resuscitative requirements, and long-term pain management. Systematic search identified 1092 unique records, and 129 met inclusion criteria. Reports of 37 FTs in the literature informed the following anesthetic axes: donor pre- and intraoperative management during facial allograft procurement, recipient perioperative care, immunotherapy, antimicrobial prophylaxis, and pain management. Quantitative synthesis of 30 articles showed a median operative time of 18 hours (range, 9–28) and fluid replacement with 13 L (5–18) of crystalloids, 13 units (0–66) of packed red blood cells, 10 units (0–63) of fresh frozen plasma, and 1 unit (0–9) of platelets.

Conclusions: Anesthetic considerations in FT span the continuum of care. Future efforts should guide standard reporting to establish evidence-based strategies that promote quality improvement and patient safety. *(Plast Reconstr Surg Glob Open 2020;8:e2955; doi: 10.1097/GOX.0000000000002955; Published online 17 August 2020.)*

INTRODUCTION

The success of facial transplantation (FT) depends on a multidisciplinary approach highlighted by cadaveric rehearsals, research procurements, and extensive clinical preparation.[1–5] The anesthesia team plays an integral role in the perioperative and intraoperative management of allograft donors and recipients, comprising up to 12% of total FT costs.[6,7] The influence of anesthetic considerations on morbidity and mortality in vascularized composite allotransplantation (VCA) has been highlighted through evaluation of upper extremity transplant anesthetic protocols that reduced perioperative bleeding and shortened hospital stay, as well as lessons learned from challenges of quadruple limb transplantation and combined face and hand transplantation.[8–10]

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Limited evidence exists to guide patient safety and quality improvement efforts. Edrich et al[11] surveyed lead anesthetists on anesthesia duration, intraoperative management, and acute complications. Discussion of anesthetic considerations is otherwise scarce in the literature despite the field's evolution with over 40 FTs performed worldwide.[1,12–20] The goal of this study was to present an institutional anesthesia protocol and variables for 2 facial allograft donors and recipients, define reported anesthetic considerations in FT, and provide a comprehensive update to inform future directions of the field.

METHODS

Institutional Experience

Institutional Review Board approval (s14-00550; clinicaltrials.gov, NCT02158793) was obtained, and informed consent was given by FT recipients and their donors' families. An institutional "FT Anesthesia Protocol," including a donor transfer algorithm, was developed.[21] Cadaveric simulations and a research procurement were performed to educate team members and plan procedures.[3,4]

Search Methods

Guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PubMed/Medline, Embase (Ovid), and CINAHL (EBSCOhost) databases were searched from inception to February 3, 2020 (Table 1).[22,23]

Selection Criteria

Two reviewers independently screened titles and abstracts to include all clinical articles with FT recipient and/or donor-specific preoperative, intraoperative, and relevant postoperative variables, including intensive care and pain management. Reference lists of relevant articles were reviewed to identify any additional articles. Non–English-language articles or those involving nonhuman subjects were excluded.

Data Collection

Full-text articles were reviewed. A tool for data collection organized by FT recipient was prospectively developed and used to record anesthetic variables, including donor status, anesthesia team composition, fluid management and resuscitation, blood loss, use of vasopressors, ventilation, operative time, anticoagulation regimen, anesthetic induction and maintenance agents, perioperative laboratory studies, induction and maintenance immunosuppression, antimicrobial prophylaxis, intensive care management and length of stay, and pain assessment and management. At the completion of data charting, a qualitative synthesis was performed by organizing available evidence into representative categories: donor and recipient preoperative and intraoperative management, as well as recipient postoperative intensive care, immunotherapy and antimicrobial prophylaxis, pain management, and long-term anesthetic considerations. A narrative synthesis was constructed based on all reported cases and corresponding anesthetic variables.

Statistical Analysis

Quantitative anesthesia–related variables reported for most FT recipients were synthesized as median and range (minimum–maximum). The data were also stratified by allograft type (partial or full FT) and most common surgical indications (ballistic trauma, burn, neurofibromatosis, and animal attack) because these were predicted to potentially influence fluid resuscitation, operative duration, and ICU duration. Further statistical or meta-analyses were not performed due to the significant risk of bias of missing data and heterogeneity of participant characteristics and surgical procedure.

Table 1. Systematic Search Strategy

Search Terms Used in Databases		
PubMed/Medline	**Embase (Ovid)**	**CINAHL (EBSCOhost)**
"Facial transplantation" [MeSH:no exp]	"Facial transplantation".mp. or *facial transplantation/	"Facial transplantation" MH
"Face transplant*" [tw]	"Face transplant".mp.	Face transplant TW
"Facial transplant*" [tw]	"Facial transplant".mp.	Facial transplant TW
"Face transplantation" [tw]	"Face transplantation".mp.	Face transplantation TW
"Facial transplantation" [tw]	"Face allotransplantation".mp.	Facial transplantation TW
"Face allotransplantation" [tw]	"Facial allotransplantation".mp.	Face allotransplantation TW
"Facial allotransplantation" [tw]	"Facial vascularized composite allotransplantation".mp.	Facial allotransplantation TW
"Facial vascularized composite allotransplantation" [tw]	"Face vascularized composite allotransplantation".mp.	Facial vascularized composite allotransplantation TW
"Face vascularized composite allotransplantation" [tw]	"Face vascularized composite allograft".mp.	Face vascularized composite allotransplantation TW
"Face vascularized composite allograft" [tw]	"Facial vascularized composite allograft".mp.	Face allograft TW
"Facial vascularized composite allograft"	"Face allograft".mp.	Facial allograft TW
"Face allograft" [tw]	"Facial allograft".mp.	Face composite tissue allotransplantation TW
"Facial allograft" [tw]	"Face composite tissue allotransplantation".mp.	Facial composite tissue allotransplantation TW
"Face composite tissue allotransplantation" [tw]	"Facial composite tissue allotransplantation".mp.	Face composite tissue allograft TW
"Facial composite tissue allotransplantation" [tw]	"Facial composite tissue allograft".mp.	Facial composite tissue allograft TW
"Face composite tissue allograft" [tw]	"Face composite tissue allograft".mp.	Face vascularized composite allograft TW
"Facial composite tissue allograft" [tw]		Facial vascularized composite allograft TW

MH, MeSH Headings; TW, text words.

RESULTS

Case Description

Anesthesia team composition included up to 4 anesthetists and 2 residents per operating room. Supine positioning and forced-air warming blankets were used. Vascular access included radial and femoral arterial lines and femoral central venous catheters.

Facial Allograft Donors

Figure 1 depicts operating room setup and team positioning. Table 2 outlines donor characteristics and preoperative status.

Donors A and B, corresponding to recipients A and B, respectively, were 26 and 23-year-old men transferred from outside institutions following brain death. Their families granted permission for facial and solid organ procurement. Upon arrival, they were assigned American Society of Anesthesiologists class 6. The head of bed was angled at 30°, and body temperature was maintained at 36°C–37.5°C, with mean arterial pressure (MAP) ≥60 mm Hg, urine output (UOP) ≥0.5 mL/kg/h over 4 hours, and central venous pressure 4–10 mm Hg. Lung-protective ventilation was maintained. Vasopressin was titrated to UOP and MAP. Levothyroxine infusion, methylprednisolone, and antimicrobial prophylaxis were administered. Preoperative imaging included computed tomography (CT) cerebral angiography, formal angiography, noncontrast CT chest/abdomen/pelvis, and echocardiography. For donor B, diagnostic bronchoscopy was performed based on previous experience.[24] Facial impression was taken for silicone mask fabrication for donor A, whereas 3-dimensional printing technology was used for donor B.

General anesthesia was administered with isoflurane, paralysis with neuromuscular blockers, and analgesia with fentanyl. An 8.0-cuffed tracheostomy was placed preoperatively. At the start of organ procurement, intravenous indocyanine green was given for visualization of facial perfusion. The technical details of the surgical procedure have been previously described.[3,4,16,25] The patients' UOPs and MAPs were maintained at goal (Fig. 2) with vasopressin 0.02–0.04 units/min and phenylephrine boluses as appropriate. Levothyroxine and antimicrobial prophylaxis were continued intraoperatively with the addition of insulin infusion (1–4 units/h) for donor B. Indocyanine green was again administered before procurement of the facial allograft, and 30,000 units of intravenous heparin were given before division of facial allograft pedicles. The procedure summary is documented in Table 3.

Facial Allograft Recipients

Recipient A, a 41-year-old man, sustained extensive burns without smoke inhalation injury in 2001. He had an uncuffed tracheostomy on presentation and had undergone 70 reconstructive procedures. Preoperative pain assessment revealed 4–6/10 pain (9/10 without medication) with intermittent tension in a "mask-like" facial distribution, controlled with oxycodone and muscle relaxants. An opioid contract was made before FT, and one provider addressed pain management for continuity of care.

Recipient B, a 25-year-old man, sustained a self-inflicted gunshot wound in 2016. He underwent several reconstructive procedures and presented with severe functional deficits and exposed facial hardware. He suffered from the chronic pain syndrome, with bitemporal headaches radiating behind his eyes without related neurologic deficits, and presented with a pain regimen of oxycodone solution, acetaminophen, and gabapentin. Pain score was 2–5/10.

Preoperative Preparation and Intraoperative Management

Tracheostomy, gastrostomy, head/neck CT, formal angiography, and medical work-up were completed in preparation of FT.[26] Recipient B underwent additional surgical care for facial fractures and hardware removal before FT.

A wire-reinforced endotracheal tube was placed through tracheostomy, and volume-controlled ventilation was used. Anesthesia was induced with propofol, fentanyl, midazolam, and a neuromuscular-blocking agent. Recipient A had an extensive surgical history and chronic pain, and reported having had 2 prior incidents of

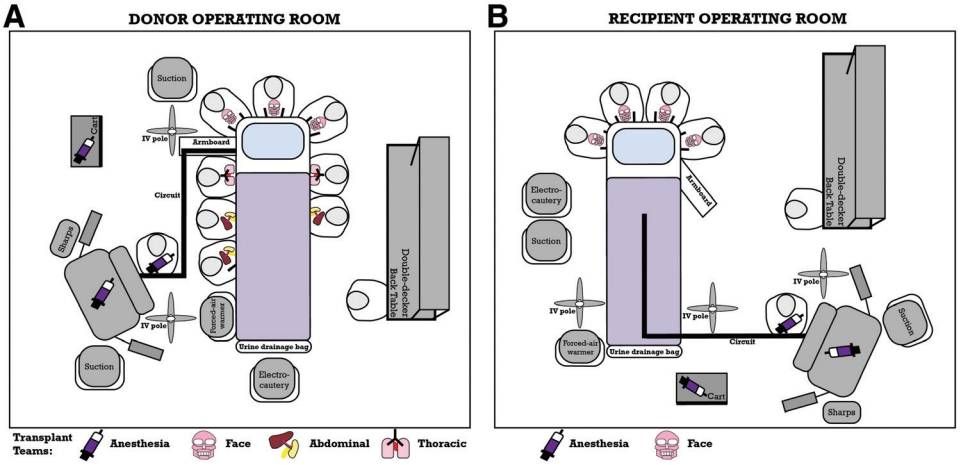

Fig. 1. General schematic of the (A) donor and (B) recipient operating rooms with placement of the anesthesia team. Printed with permission and copyrights retained by Eduardo D. Rodriguez, MD, DDS. IV indicates intravenous.

Table 2. Donor Characteristics and Preoperative Status

	Donor A	Donor B
Age (y)	26	23
Sex	Male	Male
Blood type	O+	O+
Serologies	CMV+ | EBV+	CMV− | EBV−
BMI	24.9	34.9
Weight (kg)	86	120
Medical history	Traumatic brain injury s/p 2 craniotomies for hematoma evacuation; brain death; secondary hypothyroidism	Substance use; psychiatric illness; hepatitis/ hepatosteatosis; brain death
ASA classification	6	6
Hematology	Hgb 6.8 | Hct 21.3	Hgb 8.2 | Hct 24.4
Coagulation	PT 16.0 | INR 1.4	PT 14.1 | INR 1.2
Metabolic	Na 148 | K 3.6 | Cl 112 | Ca 9.6 BUN 21 | Cr 0.5| Gluc 177	Na 149 | K 3.7 | Cl 117 | Ca 7.7 BUN 32 | Cr 1.1 | Gluc 117
Hepatic	ALT 94 | AST 24 | Alk Phos 131 | Alb 2.5	ALT 134 | AST 169 | Alk Phos 154 | Alb 2.6
pH/lactate (mmol/L)	7.39/1.2	7.32/0.6
MAP at procedure start	100 mm Hg	120 mm Hg
CVP at procedure start	9 mm Hg	18 mm Hg
Temperature (°C)	36.3	36.9

Alb, albumin; Alk Phos, alkaline phosphatase; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Ca, calcium; Cl, chloride; CMV, cytomegalovirus; Cr, creatinine; Gluc, glucose; CVP, central venous pressure; EBV, Epstein-Barr Virus; Hct, hematocrit; Hgb, hemoglobin; INR, international normalized ratio; K, potassium; Na, sodium; PT, prothrombin time; s/p, status post; Toxo, toxoplasma.

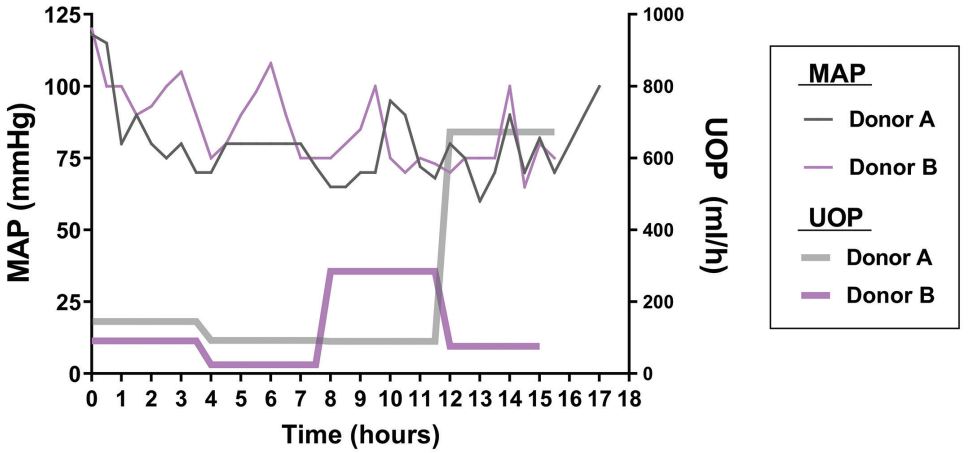

Fig. 2. Donor intraoperative monitoring of UOP and MAP. This figure was made using Prism 7.04 (GraphPad Software, La Jolla, Calif.).

awareness under anesthesia. He was maintained with isoflurane (0.4%–0.8% expired concentration), midazolam 2 mg/h, fentanyl 0.5–2.5 μg/kg/h, and vecuronium 30–40 μg/kg/h. End-tidal carbon dioxide ($Etco_2$) and positive end-expiratory pressure were 31–42 mm Hg and 3–8 cm H_2O, respectively. Multiple boluses of phenylephrine and 1 infusion at 15 μg/min were required. Insulin infusion kept glucose <180 mg/dL. Although the use of throat packs and frequent suctioning were employed, one brief episode of intraoperative desaturation occurred, and clotted blood was suctioned from the tracheostomy. Perioperative antibiotic prophylaxis consisted of cefazolin and clindamycin.

Recipient B's anesthesia was maintained with sevoflurane (1.1%–2.8% expired concentration), ketamine 1–2 μg/kg/min, and fentanyl 1–2 μg/kg/h. $Etco_2$ was 28–43 mm Hg, and positive end-expiratory pressure was 2–7 cm H_2O. Surgeons requested controlled hypotension during initial neck dissection (MAP, <65 mm Hg; central venous pressure, <5 mm Hg). After vessel anastomosis, MAP was ≥60 mm Hg. Perioperative antimicrobial prophylaxis was cefazolin, metronidazole, clindamycin, and micafungin.

Both patients received induction and maintenance immunosuppression therapy as previously described.[16,25,27] Recipient characteristics and pre- and postoperative laboratory values are outlined in Table 4. Intraoperative MAPs and UOPs are shown in Figure 3, and the procedure summary and fluid requirements in Table 5.

Postoperative Intensive Care Management

Patients arrived ventilated and sedated. The allograft was monitored closely. Goals were MAP >60 mm Hg, hematocrit >25%, and platelets >75,000. Antimicrobial prophylaxis was tailored to postoperative cultures. An insulin sliding scale was used for hyperglycemia, pantoprazole for gastrointestinal prophylaxis, and subcutaneous heparin and sequential compression devices for deep vein thrombosis (DVT) prophylaxis. Due to a history of hypertension, recipient A had a goal systolic blood pressure <140–160 mm Hg controlled with amlodipine. The

Table 3. Donor Procedure Summary of Procedure Times, Total Urine Output, and Fluid Replacement

	Donor A	Donor B
Facial allograft procurement time (h)	12	10
Total procurement time (h)	17.5	16
Total urine output (L)	4.5	2.0
Crystalloid infusion (L)	8.95	7.6
Albumin (g)	25	—
pRBC	9	7
FFP	2	3
Platelets	—	1

FFP, fresh frozen plasma.

pain management team maintained recipient A on hydromorphone patient-controlled analgesia (PCA) with standing enteral basal rate in addition to acetaminophen and a muscle relaxant per his home regimen. He continued to have a high opioid requirement, and alternatives were limited by medication interactions. $Etco_2$ levels were monitored closely. He was later transitioned to oxycodone 30 mg every 4 hours, although 3 revision procedures required intermittent reintroduction of PCA.

Recipient B's acute postoperative pain was managed with fentanyl PCA. On the first postoperative day, he underwent hematoma evacuation. Early complications also included palate and floor of mouth dehiscence requiring revision, with subsequent appropriate recovery.[28]

Long-term Pain Management

Recipient A continued to experience an intractable pain. He was admitted for regimen optimization. In collaboration with psychiatry colleagues, oxycodone was tapered by uptitrating clonidine and trialing ketamine infusions. He was successfully transitioned to buprenorphine–naloxone 8–2 mg 3 times daily with subsequent tapering.

Recipient B's facial pain improved from 7/10 postoperatively to 2/10 by 11 months posttransplant. Oxycodone–acetaminophen was subsequently tapered.

Systematic Review

A total of 1092 articles were screened, and 129 met inclusion criteria, describing 37 FT cases (Fig. 4). Qualitative analysis delineated the following essential axes to develop a narrative synthesis: donor preparation and facial allograft procurement, donor and recipient preoperative and intraoperative management, immunotherapy and antimicrobial prophylaxis, as well as recipient postoperative intensive care and pain management. Reported trends of operative time, fluid resuscitation, and length of stay are documented in Table 6 and stratified by allograft type and indication for surgery (Table 7).[1,16–18,20,29–43] The evidence synthesized was obtained from prospective case series, representing the best available clinical evidence in the FT literature. Table 8 summarizes the anesthetic considerations in FT based on our institutional experience and supported by representative references from the literature review.[1,2,4,5,11,16–21,24–27,30–40,42,44–92] These are elaborated on in the narrative synthesis summarized in the Discussion section of this article.

DISCUSSION

Donor Preparation and Facial Allograft Procurement

Facial allograft procurement requires an understanding of anesthetic considerations in solid organ recovery. The majority of facial allograft donors have suffered from brain death with procurement in a heart-beating donor, although less commonly, procurement has also occurred after cardiac cessation.[30,33,67,83] The feasibility and safety of beginning

Table 4. Recipient Characteristics and Pre- and Postoperative Laboratory Values

	Recipient A		Recipient B	
Age (y)	41		25	
Sex	Male		Male	
Blood type	O+		O+	
Serologies	CMV+ | EBV+		CMV– | EBV–	
BMI	30.0		20.8	
Weight (kg)	94.9		71.5	
Medical history	Thermal burn, hyperlipidemia, hypertension, chronic pain		Ballistic trauma, former smoker, depression, chronic pain	
Extent of defect	Scalp, forehead, eyelids, nose, cheeks, lower face, ears, lips, neck		Midface, nose, maxilla, mandible, lips	
Allograft type	Full		Partial	
Allergies	None		Amoxicillin	
ASA	3		3	
	Preoperative	Postoperative	Preoperative	Postoperative
Hematology	Hgb 14.1 | Hct 41.3	Hgb 7.0 | Hct 19.3	Hgb 12.0 | Hct 35.3	Hgb 8.8 | Hct 23.9
Coagulation	PT 13.2 | INR 1.1	PT 15.4 | INR 1.3	PT 15.3 | INR 1.3	PT 25.6 | INR 2.2
Metabolic	Na 134 | K 4.0 | Cl 100 | Ca 9.2 BUN 13 | Cr 0.9 | Gluc 91	Na 136 | K 4..0 | Cl 101 | Ca 8.6 BUN 11 | Cr 0.7 | Gluc 136	Na 138 | K 4.3 | Cl 98 | Ca 9.4 BUN 25 | Cr 0.7 | Gluc 78	Na 130 | K 4.4 | Cl 97 | Ca 7.9 BUN 13 | Cr 0.6 | Gluc 172
Hepatic	ALT 34 | AST 29 Alk Phos 65 | Alb 3.8	ALT 27 | AST 20 Alk Phos 25 | Alb 2.4	ALT 74 | AST 34 Alk Phos 75 | Alb 4.4	ALT 32 | AST 38 Alk Phos <25 | Alb 2.4
pH/lactate	7.36/1.3	7.41/1.4	7.41/0.8	7.40/1.6
MAP (start/end)	109 mm Hg	85 mm Hg	65 mm Hg	61 mm Hg
CVP (start/end)	6 mm Hg*	10 mm Hg*	19 mm Hg	9 mm Hg
Temperature (°C)	36.6	35.9	36.5	37.6

*PPV instead of CVP documented.

Alb, albumin; Alk Phos, alkaline phosphatase; ALT, alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Ca, calcium; Cl, chloride; CMV, cytomegalovirus; Cr, creatinine; CVP, central venous pressure; EBV, Epstein-Barr virus; Gluc, glucose; Hct, hematocrit; Hgb, hemoglobin; INR, international normalized ratio; K, potassium; MAP, mean arterial pressure; Na, sodium; PPV, pulse pressure variation; PT, prothrombin time; Toxo, toxoplasma.

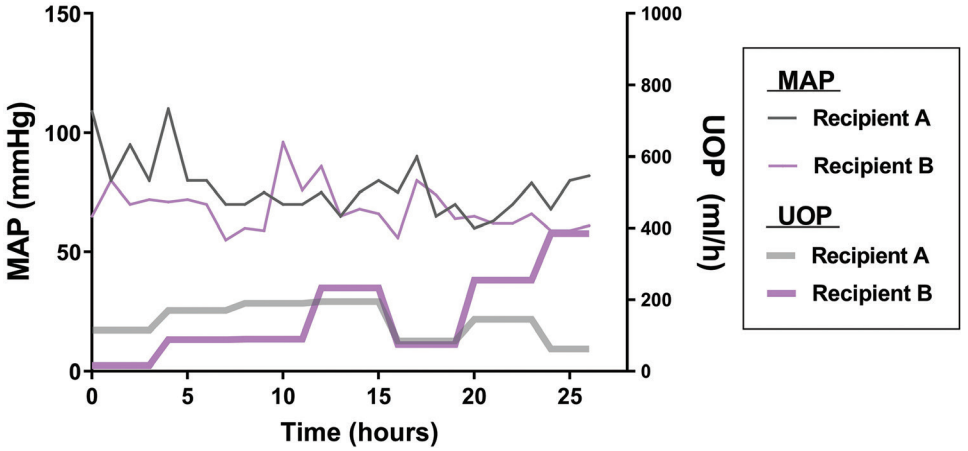

Fig. 3. Recipient intraoperative monitoring of UOP and MAP. This figure was made using Prism 7.04 (GraphPad Software, La Jolla, Calif.).

Table 5. Recipient Procedure Summary of Duration of Surgery, Fluid Resuscitation, and Length of Stay

	Recipient A	Recipient B
Duration of surgery (h)	26	25
Estimated blood loss (L)	6	4
Total urine output (L)	3.9	4.6
Crystalloid infusion (L)	18	15.5
Albumin (g)	137.5	152.5
pRBC	13	17
FFP	11	6
Platelets	2	2
ICU length of stay (d)	51	23
Total hospital length of stay (d)	62	37
Tracheostomy duration (d)	241	150

FFP, fresh frozen plasma.

facial dissection before solid organ procurement have been extensively demonstrated with no negative implications on the outcomes of solid organ transplants.[44,50,67,68]

Donor Preoperative Management

The physiologic response to brain death is complex, but improved understanding has optimized the number of viable organs procured per donor.[93] Table 9 highlights donor management goals and recommended interventions recommended by the organ system based on published consensus statements and reviews.[93–97] Institutional protocols continue to evolve with the worldwide experience. Examples include the addition of antipseudomonal agents to antimicrobial prophylaxis, and a routine preoperative bronchoscopy to rule out undiagnosed respiratory tract infection.[24,74]

Donor preparation has been shown to decrease general anesthesia time.[44] Preoperative tracheostomy can be performed at a preliminary stage in anticipation of FT, or as the first step of the procurement procedure.[1,17,25,38,44,45] Due to previous concerns of tracheostomy potentially interfering with lung procurement, facial allograft procurement with endotracheal intubation has also been described.[46,50,51] Preoperative CT cerebral angiography, formal angiography, mask production, and placement of radial artery and femoral venous catheters are other essential preparatory steps.[44,46,63,64] Donor selection and preparation must occur within a certain distance from the FT center to control for ischemia time; this highlights the importance of sufficiently stabilizing the donor for travel and controlling for transit-associated risks.[21,47,52] To date, facial allograft donors have all been sex matched, and ages have ranged from 18 to 65 years.[33,65]

Donor Intraoperative Management

Anesthetists are positioned within communication distance from all procurement teams (Fig. 1). This improved from earlier arrangements that limited access to the lower body, preventing simultaneous VCA and solid organ procurement.[2] Teams practice the flow of the donor operation to recreate this setup before FT.[4,52,53] Graft procurement experiences have been described and even practiced before FT.[2,4,44–46,50,52,53] One allograft procurement approach is "face-first, concurrent completion," where the procedure begins with facial procurement and allows each additional organ procurement to conclude shortly after donor heparinization.[44] Other strategies have included various cannulation and in situ cooling techniques to recover the facial allograft after solid organs.[1,46,50,83]

Facial allograft procurement time (range, 4.3–13.3 hours for partial, 4–12 hours for full facial allografts) depends on the recipient defect and efforts to decrease ischemia.[1,16,25,33,34,44,45,54,65,67,75] Maintenance of hemodynamic stability and euvolemia in solid organ and facial allograft procurement is particularly challenging. Despite efforts to ensure meticulous hemostasis, donor coagulopathy is not uncommon.[53] Blood loss can be most prominent during scalp dissection and skeletal osteotomies, and after initiation of abdominal organ recovery.[4,53] Despite these challenges, meticulous planning has resulted in successful recovery of up to 11 organs and tissues from a single donor.[68] Donor facial integrity is restored with a silicone-based or, more recently, a 3-dimensionally printed mask, eliminating the need for an invasive impression procedure.[69–71]

Facial Allograft Recipients

Anesthetists consent patients for general anesthesia, including the risk of death and the high likelihood of

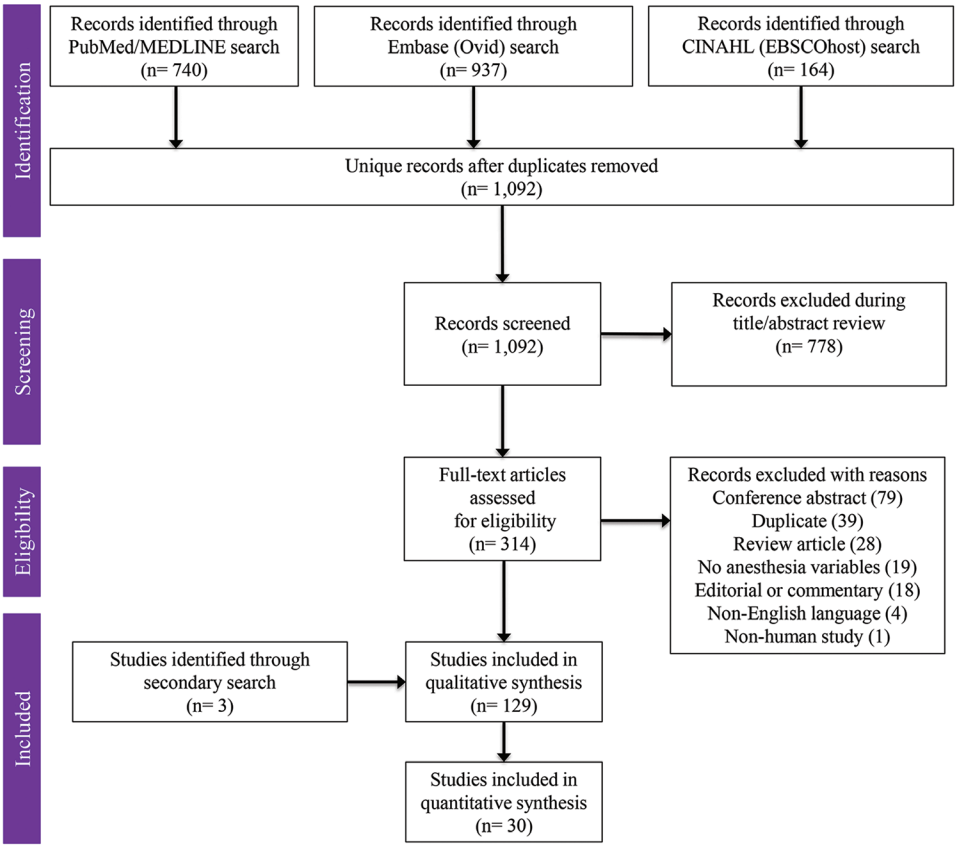

Fig. 4. PRISMA diagram for article selection. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CINAHL, Cumulative Index to Nursing and Allied Health Literature.

Table 6. Summary of Available Data from Reported Cases in the Literature

	Literature Review	
	N	Median (Range)
Recipient age (y)	42	34 (19–64)
Sex	43	35 males, 8 females
Allograft type	43	26 partial, 17 full
Allograft procurement time (h)	20	6 (4–13.3)
Operative time (h)	33	18 (9–28)
Crystalloid infusion (L)	15	13 (5–18)
pRBC	26	13 (0–66)
FFP	19	10 (0–63)
Platelets	15	1 (0–9)
ICU length of stay (d)	24	8 (1–65)

FFP, fresh frozen plasma.

blood product transfusion.[98] Reported operative times show a significant variation (range, 9–28 hours), exposing recipients to further complications under prolonged anesthesia.[1,16,17,20,29–41,43]

Recipient Preoperative Management

FT indications have included ballistic trauma, burn, animal attacks, trauma resulting from machinery, blunt trauma followed by necrotizing inflammation, neurofibromatosis, vascular tumor, cancer/radiation therapy, or recently, chronic rejection of a primary facial allograft.[12,99] Recipient age has ranged from 19 to 64 years at the time of transplantation.[28,37] Significant medical comorbidities have included hepatitis C infection (stable viral loads after alpha-interferon and ribavirin), HIV infection (on highly active antiretroviral therapy, CD4 >400/mL, negative viral load), hypertension, non–insulin-dependent diabetes mellitus, granulomatosis with polyangiitis associated with pyoderma gangrenosum, generalized epilepsy, surgically clipped cerebral aneurysm, glaucoma, cardiac septal hypokinesia on echocardiography, and lower extremity phlebitis.[17,32,72,76,83,100] Other comorbidities have included a history of alcohol and substance use disorders, smoking history, posttraumatic stress disorder, major depressive disorder, and bipolar disorder.[32,61,77,101] Pretransplant reconstructive surgical histories are typically extensive with the exception of one case of immediate FT.[39]

Many patients have histories of difficult airways. Mouth opening can be limited by burn scar contractures or trauma-related trismus, and obstruction can occur from soft-tissue ptosis.[55–59] Many patients present with a tracheostomy in place, whereas others have required tracheostomy pre-, intra-, or even postoperatively.[11,17,37,66] Early tracheostomy can reduce FT operative time and minimizes airway complications.

Recipient Intraoperative Management

Meticulous care is taken to preserve hemodynamic stability and hemostasis, prevent pressure injury by

Table 7. Summary of Available Data from Reported Cases in the Literature Stratified by Allograft Type and Surgical Indication

	Partial FT (n = 26)		Full FT (n = 17)		Ballistic Trauma (n = 21)		Burn (n = 10)		Neurofibromatosis (n = 4)		Animal Attack (n = 3)	
	n	Median (Range)	n	Median (Range)	n	Median (Range)	n	Median (Range)	n	Median (Range)	n	Median (Range)
Allograft procurement time (h)	12	8.1 (4.3–13.3)	8	4.8 (4–12)	9	9 (4.5–12)	7	6 (4–12)	2	4.9 (4.3–5.6)	1	4 (–)
Operative time (h)	20	18.5 (11–28)	13	17 (9–26)	15	18 (11–26)	8	16.5 (9–28)	4	20.3 (15–24)	3	18 (15–19)
Crystalloid infusion (L)	9	13 (5–17)	6	12 (8–18)	8	12 (5–16)	4	13 (8–18)	2	13 (–)	0	—
pRBC	14	10 (0–66)	12	13 (2–27)	12	13 (0–20)	7	5 (2–66)	4	26 (22–28)	2	13 (6–20)
FFP	10	8 (2–63)	9	11 (0–16)	9	6 (2–16)	5	11 (0–63)	3	13 (2–23)	1	16 (–)
Platelets	9	2 (0–9)	6	1 (0–7)	6	2 (0–7)	4	2 (0–9)	3	1 (1–3)	1	0 (–)
ICU length of stay (d)	14	12 (1–65)	10	6 (2–51)	11	9 (2–23)	7	4 (2–65)	3	12 (7–47)	1	18 (–)

FFP, fresh frozen plasma.

Table 8. Summary of Anesthetic Considerations in Facial Transplantation Based on Our Institutional Experience and Literature Review

Preoperative Considerations	Supporting Literature*
• Development of a "Face Transplant Anesthesia Protocol"	[1,5,17,18,20,44–49]
• Team cadaveric simulations and/or research procurement rehearsals	[1,2,4,5,16,31,32,38,45,48,50–54]
Recipient	
• Evaluation of anesthetic, surgical and medical histories, risk of bleeding, possibility of difficult airway	[1,17,18,32,34,40–42,55–60]
• Pain management evaluation, particularly assessment of chronic pain	[61,62]
• Establishment of central and peripheral vascular access and monitoring	[5,11,17,20]
• Additional procedure(s): tracheostomy, gastrostomy, CT head/neck, formal angiography, reconstructive procedures in preparation for transplantation	[1,11,16–18,25,26,32,34,37, 38,41,42,47,60,63–66]
Donor	
• Management protocol for heart-beating brain-dead donors	[1,4,20,25,34,44–46,54,67,68]
• Monitoring during transfer from an outside hospital	[4,16,21,25]
• Establishment of central and peripheral vascular access and monitoring	[5,20,25,46]
• Additional procedure(s): tracheostomy, bronchoscopy, CT chest/abdomen/pelvis, echocardiography, solid organ biopsies, CT cerebral angiography, formal angiography, mask production	[1,2,4,16,17,24–26,34, 38,42–45,47,63–65,69–71]
Intraoperative Considerations	
• Coordination between recipient and donor rooms	[1,16,32,37,39,40,43,45,51,53]
Recipient	
• Prevention of pressure injury by offloading and appropriate padding	[5]
• Regular suction with placement of throat packs to avoid airway occlusion	
• Maintenance of body temperature using lower and underbody forced-air warming blankets	[17,18]
• Anticipation of blood loss particularly during allograft reperfusion	[11,17,30,33,35,46,52,65,72,73]
• Controlled hypotension (case and surgeon-specific)	[17,20]
• Administration of induction immunosuppression and antimicrobial prophylaxis	[1,17,20,25,27,32,34–39,42,43,54,74–80]
Donor	
• Planning for prolonged allograft procurement time	[1,16,25,33,34,44,45,54,65,67,75]
• Positioning within communication distance of all procurement teams	[5,44–46]
• Management protocol for "face-first" procurement from heart-beating brain-dead donors	[1,5,44,45,50,52,67]
• Maintenance of body temperature using lower and underbody forced-air warming blankets	
• Anticipation of blood loss particularly during skeletal osteotomies and after initiation of abdominal organ recovery	[4,25,45,53]
Acute Postoperative Considerations	
• Administration of immunosuppression, antimicrobial, and antithrombotic prophylaxis	[1,5,17,25,27,31,32,34–40,42,43, 65,66,74–84]
• Elevation of head of bed >30° with frequent allograft monitoring for viability or rejection	[5,19,20,32]
• Multimodal pain management with close monitoring of end tidal CO_2 levels	[19,32,62]
• Implementation of a rehabilitation protocol	[5,31,39,40,47,66,85–87]
Long-term postoperative considerations	
• Outpatient pain management strategy and follow-up	[88–90]
• Planning for revision procedures as needed	[77,91,92]

*Supporting literature highlights select representative references from the facial transplantation literature review that are elaborated on in the narrative synthesis.
CO_2, carbon dioxide; CT, computed tomography.

offloading, and avert airway occlusion. Median operative time in the literature is 18 hours (range, 9–28) with fluid replacement, including a median crystalloid infusion of 13 L (range, 5–18 L), 13 units of packed red blood cells (pRBCs) (range, 0–66 units), 10 units of fresh frozen plasma (range, 0–63 units), and 1 unit of platelets (range, 0–9 units) (Table 6).[1,16–18,20,29–43] Few reports describe the use of fibrinogen for hemostasis or colloids such as albumin for volume repletion.[18,20,33,42,102] A survey-study of lead anesthesiologists involved in the first fourteen FT cases

Table 9. Donor Physiologic Responses after Neurologic Determination of Death, Management Goals, and Recommended Intervention by Organ System[93–97]

System	Physiologic Responses	Management Goals	Recommended Intervention
Cardiovascular	• Initial hypertensive crisis followed by hypotension • Arrhythmia secondary to metabolic derangements	• MAP ≥60 mm Hg • CVP 4–10 mm Hg • HR 60–120 beats/min • Left ventricular ejection fracture ≥45% • ≤1 vasopressor and low dose (eg, dopamine ≤10 μg/kg/min)	• Nitroprusside or esmolol for initial hypertension • Vasoactive agents to maintain hemodynamic goal and organ perfusion: dopamine, vasopressin (refractory shock), norepinephrine, phenylephrine, dobutamine, epinephrine (severe shock)
Respiratory	• Pulmonary edema	• Pao_2/Fio_2 ratio >300 mm Hg • pH value from arterial blood gas 7.3–7.45	• Use lung-protective ventilation (eg, small TV 6–8 mL/kg, low Fio_2, high PEEP 8–10 cm H_2O) • Begin with lung recruitment maneuvers • Elevate head of bed to reduce risk of aspiration • Consider diuretics if marked fluid overload
Renal	• Vascular constriction resulting in AKI	• Urine output over 4 h ≥ 1 mL/kg/h	• Goal is euvolemia using CVP, PAOP, or PPV and SVV with preferably crystalloid
Endocrine	• Hyperglycemia • Vasopressin deficiency • Corticosteroid deficiency • Hypothyroidism	• Glucose level <150 mg/dL*	• Insulin infusion to goal glucose • Consider vasopressin replacement • High-dose corticosteroids bolus then continuous infusion† • Consider thyroid replacement therapy with T3 and T4 bolus then continuous infusion
Hematologic	• Coagulopathy	• Hemoglobin level >7 g/dL	• Monitor with coagulation laboratory values and TEG • Transfuse for hemoglobin <7 g/dL • Correct coagulopathy with clotting factors (ie, FFP) or platelets if ongoing bleeding
Neurologic	• Hypothermia • Central diabetes insipidus and hypernatremia • Movements mediated by spinal reflexes	• Temperature >35°C • Serum sodium level <155 mmol/L	• Active warming to maintain temperature • Cautious correction of hypernatremia can be possible with slow, hypotonic infusion of 0.45% NaCl • Intraoperative skeletal muscle paralysis to reduce somatic response to surgical stimulus

*Hyperglycemia should be controlled based on institutional intensive care unit guidelines.
†High-dose corticosteroids should only be administered after blood has been collected for tissue typing.
AKI, acute kidney injury; CVP, central venous pressure; FFP, fresh frozen plasma; Fio_2, fraction of inspired oxygen; HR, heart rate; NaCl, sodium chloride; Pao_2, partial pressure of arterial oxygen; PAOP, pulmonary artery occlusion pressure; PEEP, positive end-expiratory pressure; PPV, pulse pressure variation; SVV, stroke volume variation; T3, triiodothyronine; T4, thyroxine; TEG, thromboelastogram; TV, tidal volume.

reported data on intraoperative catecholamine use.[11] Recipient monitoring has most frequently been performed with at least a femoral venous catheter in addition to radial and femoral arterial lines.[11,17] Preference for femoral over subclavian or internal jugular venous access is explained by concerns for thrombosis affecting venous outflow from the face and risk of pneumothorax in a long case with mechanical ventilation.[11,17]

Concerns for intraoperative blood loss are typically heightened following reperfusion of allografts procured in donors after cardiac death[30,46,52] or surgical excision of plexiform neurofibromas shown to require the most units of pRBCs among surgical indications (Table 7),[72,103] and has led to the use of a Mobile Laboratory Unit to monitor hemostasis.[73] Intraoperative cell salvage has been used to replace blood loss, in addition to transfusion of pRBCs.[35] Subcutaneous heparin is most commonly used for DVT prophylaxis.[17,32,37,66] However, a case with historical concern for heparin-induced thrombocytopenia and thrombosis led to avoidance of chemical DVT prophylaxis in the recipient and donor anticoagulation with bivalirudin.[104]

If not present before the procedure, a gastrostomy tube is placed to address postoperative nutrition.[17,32]

Recipient Postoperative Intensive Care Management

Intensive care focuses on maintaining hemodynamic stability and adequate ventilation, and monitoring for allograft viability and/or potential rejection, in addition to other postoperative complications, including postoperative delirium and infection.[5,17,19,101] Decannulation has been reported to occur between 1 week and 1 month posttransplant, with almost all tracheostomies closed by the first year posttransplant.[36,37,49,54,57,58,60,65] Enteral feeding is typically initiated after bowel sounds have resumed with subsequent oral diet advancement as tolerated, and cessation of enteral access by 12 months in most reported cases.[17,49,56,58,60]

Recipient ICU length of stay has ranged from 1 to 51 days in the literature, excluding a patient with face and bilateral hand transplant who expired after a 65-day–long complicated course.[1,16,17,20,32,35,37,39,42,48,84] Team experience is associated with reduction in the length of stay,[17] and early rehabilitation promotes recovery.[85–87]

Immunotherapy and Antimicrobial Prophylaxis

Although exact timing is not universal, anesthetists have administered at least a portion of induction immunosuppression intraoperatively. For example, corticosteroids alone or with antithymocyte globulin have been given before reperfusion of the facial allograft.[1,32,34,38,54,76] The complete induction regimen has also been administered at incision time.[36] Antimicrobial prophylaxis covering bacterial, viral, and fungal infections is particularly important in the early postoperative period when the highest incidence of infection occurs.[1,17,35,37,74,77–79,81,82]

Recipient Pain Management

Preoperative counseling can reduce postoperative use of prescription pain medications.[105–107] Preoperative management of chronic pain is warranted in FT, considering the incidence of alcohol or other substance use disorders, or long-term opioid use seen in this patient population.[61,62,108,109] The pain thermometer and visual analog scale are assessment tools with reported use in FT.[62,86,110] Quality of life surveys such as the 36-Short Form Health Survey and EuroQol-5D (EQ-5D) also incorporate pain assessments.[88,89,101,110–113] Postoperative facial nerve pain control has included oxycodone and gabapentin, or the combination of oxycodone with methadone in a patient with a history of intravenous drug use.[32,62] The extent of recovery and long hospital stay have contributed to postoperative opioid dependence and reduced quality of life. Oser et al[89] described worsened depression in association with opioid dependence, and Lemmens et al[88] described hyponatremia attributed to pain regimen interactions.[90] Deprescribing or tapering pain medications should be prioritized early to ensure adequate pain relief while preventing adverse events.[107] In our experience, this requires a multidisciplinary collaboration.

Recipient Long-term Considerations

Recipients will inevitably return for secondary revisions.[77,91,92] Although they may present with improved mouth opening and airway volume,[55,57,58] their extensive histories before FT will continue to require vigilance and proactive pain management strategies, as learned from recipient A's clinical course. Local anesthetics can be used for revision procedures when possible, and importantly, their use reflects sensory recovery.[2,30,72] Unfortunately, secondary procedures have also included allograft explantation, providing further insight into strategies for handling adverse outcomes.[13,80]

Anesthetic Challenges and Future Implications

As the field continues to evolve and attempts at more extensive procedures are undertaken, multidisciplinary collaboration remains crucial to ensuring patient safety. Anesthesia teams are challenged to find innovative solutions to manage complex scenarios such as combined VCA.[9,17,35,102] Reduction of ischemia time, prophylactic hemodialysis, and extracorporeal allograft perfusion are hypothesized solutions to improve medical management.[9] Other necessary advances include developing better tools to assess and manage pain, and preventing and treating substance dependence. Although these concerns are not exclusive to FT, they are particularly relevant to the field.

Limitations

Although we present a comprehensive review, evidence is limited to reports in the peer-reviewed literature captured by our systematic search strategy. The report of our institutional experience serves to exemplify the thorough presentation of anesthetic considerations in FT, which is infrequently disclosed. Missing quantitative data on fluid resuscitation, operative duration, and ICU duration, in addition to a limited number of cases performed in a relatively heterogeneous cohort of patients and surgical approaches, did not allow for further statistical analyses. However, to our knowledge, this study represents the most comprehensive assessment of anesthetic considerations in FT and provides a platform for future efforts to establish evidence-based strategies that promote quality improvement and patient safety.

CONCLUSIONS

Implementing a "Face Transplant Anesthesia Protocol" requires extensive preparation and vigilance throughout the continuum of care to address the challenges of prolonged operative time, difficult airway, high risk of blood loss, and tailored anesthetic management in patients with complex surgical and medical histories. These responsibilities continue postoperatively with intensive care and pain management. Optimizing anesthetic care in FT can advance reconstructive transplantation.

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