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Standardizing training protocol of an intestinal transplantation model: A learning curve study

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ABSTRACT

Experimental: Rodent models of intestinal transplantation are crucial for advancing our understanding of various biological processes related to the procedure, including ischemia-reperfusion injury, acute cellular rejection and immunological tolerance, among others. These models also provide a platform for developing strategies and therapeutics aimed at improving long-term survival, with the ultimate goal of translating laboratory findings into clinical applications. With over twenty years of experience in intestinal transplantation in rodents, our team currently achieves a survival rate of 83 % in orthotopic transplants and 85 % in heterotopic transplants—success rates comparable to those reported by leading research groups in the field. This manuscript outlines the key steps involved in achieving successful results in rat intestinal transplantation models. It covers the entire process, from basic microsurgical training and graft procurement to implantation and postoperative care of the recipient. We hope this work will serve as a valuable guide for research groups seeking to establish these experimental transplantation models in their own laboratories.

Introduction

Intestinal transplantation (ITx) models in rodents are essential for understanding the biological processes associated with the procedure. These models help address key challenges such as graft rejection, ischemia-reperfusion injury, graft versus host disease, evaluation of immunosuppression protocols, and the development of strategies to achieve immunological tolerance—topics of central importance for both clinical and research teams working on ITx [1–5].

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Although ITx can be performed in various species, rats are the most commonly used animals in ITx research, following the groundbreaking work of Mochick and Russel, who first described the procedure in rats in 1972 [6]. Since then, several groups have refined ITx techniques in rats, focusing on aspects such as learning curves, model organization, and strategies for improving outcomes. While the details of these experimental procedures vary—particularly in areas such as animal handling (e.g., anesthesia, analgesia) and microsurgical techniques (e.g., types of sutures, graft location)—each research team adapts the methodology to suit their specific capabilities and research goals [7–11].

Our microsurgery team has contributed extensively to advancing this field [12–18]. Our involvement in experimental ITx began in 2006, coinciding with the launch of the clinical program at a leading institution in ITx [19]. Since then, we have benefited from ongoing collaboration with prominent centers in experimental and clinical ITx. This collaboration has been instrumental in optimizing ITx models in rodents.

This paper aims to share our team's experience in developing the model and training various surgeons to perform the ITx model. It also reports the surgical times and complications encountered while fine-tuning the model.The training concludes, and therefore, the learning curves reported, when the surgeon achieves a 50 % survival rate, taking into account the expected initial losses in the firsts attempts.

Materials and methods

This section outlines the essential elements required to establish an experimental ITx program, providing a detailed description of the methodology used in the procedures. All procedures were performed and results were compiled from the three institutions in which the authors currently work.The standardized data collection included the surgical times for the donor surgery, the recipient surgery, and the following specific durations within the recipient surgery: arterial anastomosis, venous anastomosis, total clamping time, and the overall duration of the procedure. Additionally, there was a section for recording any complications encountered during the surgeries.

Microsurgical Techniques and Laboratory Rodent Management as Key Components for Developing Experimental ITx Procedures: Successful rodent transplantation procedures depend on the proper use of magnification tools, microsurgical instruments, and a solid formation in basic microsurgical techniques. Microsurgery training, which has been extensively documented, follows a globally accepted methodology. This training typically progresses through three stages: exercises with inanimate models, transition models, and finally, living models. Such training is critical for anyone intending to perform solid organ transplants in rodents with success.

In addition, a thorough understanding of the anatomy, physiology, and potential complications of the experimental animals is essential. Recognizing and addressing signs of animal discomfort is a vital part of this knowledge. Adhering to the ARRIVE guidelines

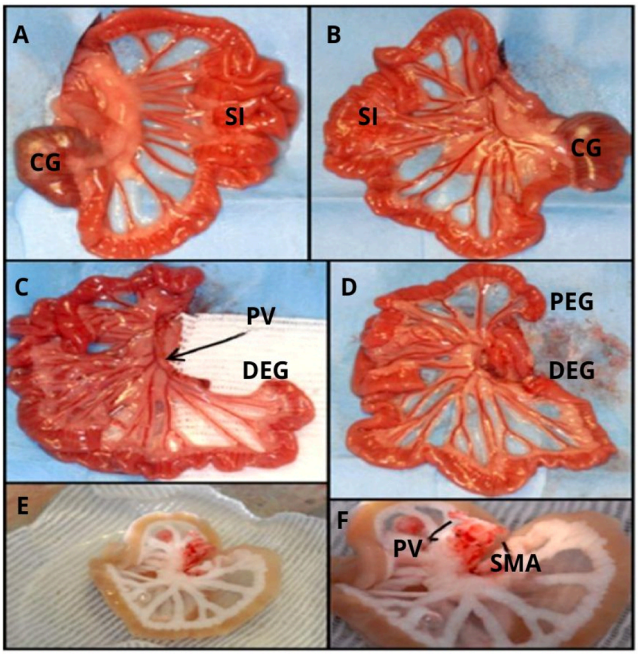

Fig. 1. Donor surgery: positioning of the small intestine (SI) and cecum glands (CG) before the rotation maneuver (A), and after the rotation (B). Selection of the distal end of the graft (DEG) and identification of the portal vein (PV) (C) Selection of the proximal end of the graft (PEG) (D). Macroscopic appearance of the graft after a proper lavage (E). Identification of the superior mesenteric artery (SMA) and the PC of the graft during the cold ischemia period (F).

ensures an improved experimental design, aligning with standardized criteria for the humane treatment of animals. This approach is key to achieving consistent, reproducible results that can be compared across different research centers [20,21].

ITx Donor procedure in rats: essential considerations for obtaining a quality graft

The donor procedure in rats involves careful animal selection, preoperative management, and a precise surgical technique to obtain a high-quality graft. While various surgical protocols for intestinal extraction are described in the literature, the goal remains the same: to harvest a graft with both arterial and venous pedicles for implantation. Thus, our team has standardized the procedure in the way described below to ensure consistent and optimal results.

Our procedure begins with pre-surgical preparation, where donor rats, weighing ideally between 200 and 290 g, are acclimated to the procedure facility for at least 72 hours before surgery. They undergo a 12-hour fasting period, with free access to water. Inhalation anesthesia is initiated in an induction chamber with 5 % isoflurane and then maintained at 1.5–2 % using a mask system. The anesthetic is volatilized through an anesthesia machine with oxygen at a flow rate of 1.5–2 liters per hour. Once the rat is under anesthesia, the abdominal area is shaved, and antisepsis is performed. Additionally, 5 ml of physiological solution and 30 mg/kg of Tramadol Hydrochloride are administered subcutaneously to ensure proper hydration and analgesia.

The surgical procedure begins with a xipho-pubic incision to access the abdominal cavity. Using a surgical microscope at 4X magnification, the ligament of Treitz is cut, and the superior mesenteric artery (SMA) is carefully dissected. The intestine is then rotated so that the small intestine is positioned to the left and the large intestine to the right of the operator (Figs. 1-A and 1-B). This maneuver helps to place the graft in an optimal position to minimize further manipulation during the surgery. Using both microsurgical instruments and a bipolar electrocoagulator, the distal end of the graft is selected and sectioned, and the ileocecocolic artery and vein are dissected, coagulated, and sectioned.(Fig. 1-C) The colon is then excluded from the graft. Subsequently, the proximal end of the graft at the jejunum level is selected and sectioned. At that point, the vessels supplying the duodenum and the part of the jejunum that was excluded from the graft are dissected, coagulated, and divided (Fig. 1-D). Next, the portal vein (PV) is dissected from the adjacent tissues; the splenic and pyloric veins are also carefully dissected, coagulated, and divided.

In the final stage of the procedure, the abdominal aorta (AA) and the inferior vena cava (IVC) are clamped, marking the beginning of the ischemic phase. The PV is sectioned, and a heparinized preservation solution (10 U/ml at 4ºC) is infused into the graft through the distal AA using a 21 G needle. The intestine should turn pale at this stage, indicating successful graft flushing. The SMA is then cut at its origin, including a small aortic patch to facilitate arterial anastomosis, and lastly the graft is placed in a cold preservation solution. (Fig. 1-E). Once on the bench, the vascular pedicle (VP and SMA) is identified to ensure proper graft positioning during implantation and to avoid any rotations (Fig. 1-F).

The cold ischemia phase is an unavoidable moment in the field of solid organ transplants. Regarding this phase of the procedure, the scientific community strives to find strategies to optimize graft preservation and extend cold ischemia times to reduce ischemia-reperfusion damage and, consequently, improve the transplanted graft functionality. While it is not the objective of this work to discuss this topic, we have evaluated the impact of cold ischemia on the graft, extracting it with the described technique and studying the histological damage kinetics at different ischemia times (data not shown) [13,15,17].

Recipient procedure in ITx

The goal of the recipient procedure is to ensure proper revascularization of the graft, promoting its viability and enabling successful postoperative survival. The steps for recipient preparation—acclimatization, animal weight assessment, anesthetic and analgesic protocols, surgical field preparation, and surgical approach—are similar to those used for donors, with the exception that recipients do not undergo solid fasting.

Fluid administration for recipients can be performed subcutaneously or intravenously through a lateral tail vein using a Teflon catheter (No. 24). A flow rate of 0.75 ml/min is maintained from the start of surgery until graft reperfusion. If the subcutaneous route is chosen, after reperfusion, an additional 3–5 ml of warm physiological solution is administered via the dorsal vein of the penis using a 30 G needle, ensuring no damage to the vein or surrounding structures.

The abdominal cavity is then accessed in the same way as in the donor surgery, and the AA and IVC are dissected at the infrarenal level. Lumbar vessels are coagulated, and the AA and IVC are clamped with a 1.5 cm gap for the vascular anastomoses. A venotomy and

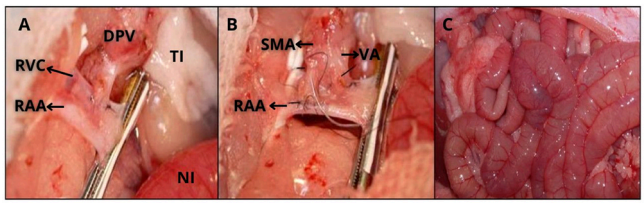

Fig. 2. Recipient surgery: A- end-to-side venous anastomosis between the recipient vena cava (RVC) and the donor portal vein (DVP). In addition, the recipient aortic artery (RAA), the native intestine (NI) and the transplanted intestine (TI) can be seen. B- arterial anastomosis between the donor superior mesenteric artery (SMA) and the RAA. The venous anastomosis (VA) is also observed. C- macroscopic appearance of the reperfused graft.

an arteriotomy is made in both the IVC and the AA respectively. An end-to-side venous anastomosis is performed between the donor portal vein (PV) and the recipient IVC, followed by an end-to-side anastomosis between the graft SMA and recipient AA. These anastomoses are completed with 8–0 or 9–0 monofilament nylon using a simple continuous suture, starting with the posterior wall and finishing with the anterior wall. Once both anastomoses are finished, the clamps are removed in sequence. If successful, the graft will transition from pale to pink as blood flow is restored (Fig. 2).

The magnification used for these vascular anastomoses depends on the surgeon, typically ranging from 10X to 25X magnification.

For both heterotopic and orthotopic transplants, the steps up to revascularization are the same. After graft reperfusion, the procedure diverges based on the type of transplant. In heterotopic transplantation, the graft is exteriorized via two ostomies on the right abdominal wall using the mucosal eversion technique with 6–0 nylon suture, typically requiring 4–6 single stitches. (Fig. 3-A) In orthotopic transplantation, the recipient's intestine is resected from the proximal jejunum to about 3–4 cm from the ileocecal valve. Two enteroanastomoses are then performed between the native intestine and the graft using 7–0 nylon monofilament (Fig. 3-B). In both cases the recipient's abdomen is closed in two layers—muscular and cutaneous—using 4–0 nylon suture, and 0.5 ml of 2 % lidocaine is applied to the surgical site.

Postoperative care is critical for successful recipient survival. Our team follows a routine analgesic protocol, administering Tramadol (30 mg/kg) every 24 hours for 72 hours post-surgery, with additional doses as needed. Ceftriaxone (50 mg/kg) is also administered for seven days starting intraoperatively. A clinical score chart is used to assess pain and discomfort, allowing us to adjust care or apply the humane endpoint when necessary. Other indirect signs of clinical discomfort are the interaction with enrichment elements (paper, tube, cookies) and the conducting of the behavioural test outside the cage: Meticulous palpation and behaviour [13,26].

Heterotopic recipients require specific care for their ostomies, including daily cleaning to prevent obstructions. This can be done without sedation, using saline-soaked swabs and forceps. Orthotopic recipients, however, must be monitored to prevent enteroanastomosis dehiscence due to the passage of food. Initially, they are provided with water and gelatin, transitioning to regular rodent food by the 4th or 5th postoperative day.

Experimental transplantation models allow the combination of different rat strains. The performance of allogeneic ITx (donor and recipient of different strains) or isogenic (donor and recipient of the same strain) has been well described by different research groups. We typically perform isogenic transplants using Wistar rats for ischemia-reperfusion studies or ITx model development. For allogeneic ITx, we use combinations of Sprague Dawley and Wistar rats or Wistar and Lewis rats to study rejection and graft-versus-host disease. These allogeneic transplants allow for more in-depth research on immune responses following ITx [12,13,16–18]. The gender of the rat is not taken into consideration during the procedure, as we perform the transplantation in both male and female rats. This approach ensures a more comprehensive analysis and enhances the generalizability of the results.

Statistics and graphical analysis

The statistical analysis was performed using the GraphPad software version 9.00 (San Diego, California, United States). The graphical abstract was created using Biorender.com [27].

Results

Five experimental surgeons were trained in microsurgery and ITx, performing over 315 donor procedures and 271 recipient surgeries (102 orthotopic and 169 heterotopic ITx) through their respective training in this microsurgical technique. This led to an extended survival rate (more than five days post-transplant) of 83 % for orthotopic ITx and 85 % for heterotopic ITx. These surgeons then went on to contribute to numerous research projects and PhD theses within our institution. Different surgeons documented their learning curves, highlighting complications encountered during both donor and recipient procedures, and defined full training as achieving sustained recipient survival of more than 50 % after initial losses. Standardizing these techniques has enabled reproducibility across different research protocols.

The systematization of these procedures has reduced donor surgery time to 49.21 ± 13.33 minutes. Continuous practice has been crucial in minimizing extraction times,showing a statistically significant difference between the first and subsequent donor procedures.

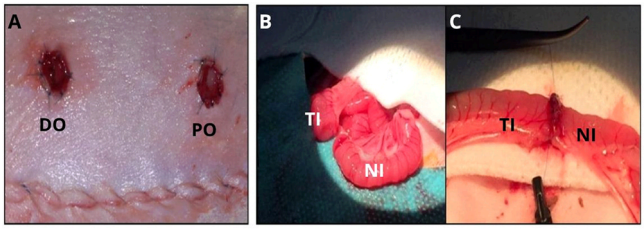

Fig. 3. A- exteriorization of the graft through the abdominal wall by making a proximal stoma (PO) and a distal stoma (DO) in the heterotopic ITx model. B and C- enteroanastomosis between the transplanted intestine (TI) and the native intestine (NI) in the orthotopic model using 7–0 monofilament nylon as suture material.

(Fig. 4).

Ischemia time, which is directly related to organ damage, was quantified using the Park index. This index helps assess graft condition at the time of implantation, depending on ischemia duration (Fig. 5-A and B). The management of ischemia time is critical in research studies, as it affects both recipient survival and the extent of post-ischemia-reperfusion injury (Fig. 5-C).

For vascular anastomosis, our team typically requires 21.34 ± 6.46 minutes for venous anastomosis and 18.18 ± 4.44 minutes for arterial anastomosis, with a total clamping time of 37.91 ± 9.11 minutes (Fig. 6). The most common complications during recipient surgery involve arterial bleeding, portal thrombosis, and SMA stenosis.(Fig. 7) Intensive and continuous training in small vessel anastomosis is crucial, as these challenges hinder successful reperfusion and recipient recovery.

The average total surgery on the recipient time is 98.5 ± 19.8 minutes for orthotopic ITx and 83.4 ± 14.1 minutes for heterotopic ITx, with significant differences between the two procedures (Fig. 6-G).

In isogenic ITx using inbred strains, we achieved prolonged survival (over 18 months) with recipients in excellent clinical condition at the time of sacrifice. In allogeneic ITx combinations without immunosuppression, graft-rejection begins to manifest around day 5 post-transplant, with mild to moderate histopathological signs of acute cellular rejection, progressing to severe rejection by days 10–12, evident in the animal's clinical state and macroscopic appearance of the transplanted intestine.

Discussion

Experimental models of ITx are essential for advancing our understanding of the biological processes associated with ITx, with the goal of improving long-term clinical outcomes. Since our establishment in 2006, our team has been dedicated to developing experimental models, particularly ITx, alongside microsurgical models [13,15–17,22].

This expertise has enabled our team to develop successful heterotopic and orthotopic ITx models in rats, achieving survival rates comparable to those reported in the literature. A landmark study by Zhong reported a 90 % survival rate in heterotopic ITx and 86 % in orthotopic ITx [23]. With this systematic approach to training our team has achieved a survival rate of 83 % for orthotopic ITx and 85 % for heterotopic ITx, demonstrating the effectiveness of the techniques we have described. This standardized training and learning experience has also made it easier to create a more reproducible model when training surgeons at different centers.

One of the limitations of this work is the incomplete recording of certain variables by some surgeons. While taking responsibility for the procedure and measuring relevant variables is an essential part of training, accurately reporting the times is crucial. A structured approach to data collection ensures more reliable post-procedure analysis and more effective error correction. This, in turn, allows for better optimization of the procedure and the development of a more consistent and reproducible model.

Due to the complexity of the ITx procedure, continuous training and a systematic approach are crucial to avoid complications that could result in graft failure or recipient death [9]. We have identified several key factors that contribute to successful ITx, including donor surgery duration, graft preservation, cold ischemia time, and the performance of vascular anastomoses during implantation.

Minimizing donor surgery time is essential for obtaining a high-quality graft. The use of a bipolar coagulator has significantly reduced the surgical time compared to suture-based methods, as demonstrated by the comparison of our donor surgery times with those reported in other studies. Donor surgeries using sutures have been reported to take up to 200 minutes, whereas our procedures, following the outlined steps, have reduced this to approximately 54.20 ± 10.73 minutes [23].

Graft preservation is also critical, as cold ischemia time directly correlates with the extent of tissue damage. Our findings, illustrated in Fig. 5, show that extending cold ischemia time increases the Park index, which reflects graft damage. We have observed that Park indices of 4 or higher during reperfusion correlate with recipient death within 48 hours [13]. These insights highlight the importance of minimizing preservation time and offer a basis for further research into new preservation solutions to extend ischemia times without compromising graft quality.

Vascular anastomoses are the most technically challenging part of the procedure and require skilled and well-trained surgeons. This is particularly critical, as improper technique can lead to thrombosis, ischemia, or graft failure. Additionally, the small size of the vessels and the complexity of suturing them under a microscope increases the risk of technical errors. Maintaining proper graft

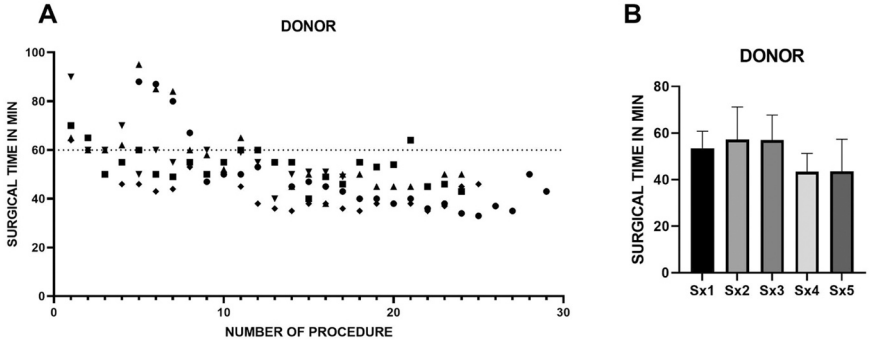

Fig. 4. Surgical times of the donor surgery (A); each point represents a procedure and each shape a surgeon (Sx). Fig. B shows the average times it takes each SX to perform the surgery.

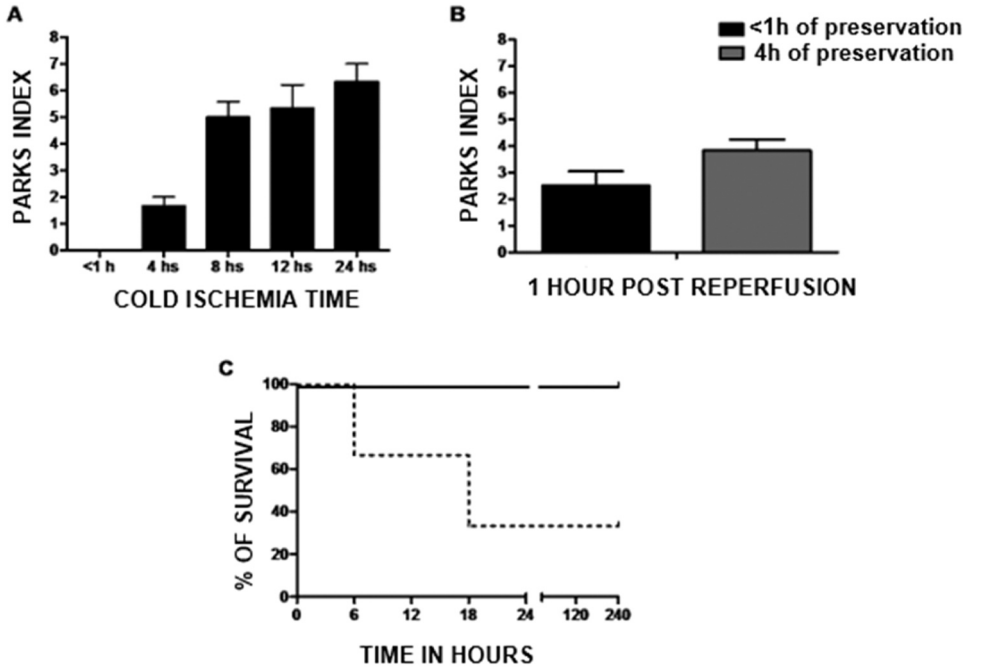

Fig. 5. Preservation time impacts graft architecture during cold ischemia (A) and the reperfusion phase (B). Histological damage was quantified using the Park scale. On the other hand, the damage caused to the graft during cold ischemia phase has an impact on the transplanted animal's survival, as shown in Figure C, when evaluating recipient animals that received intestines preserved for less than 60 minutes (continuous line) and animals that received grafts preserved for 4 hours (dotted line).

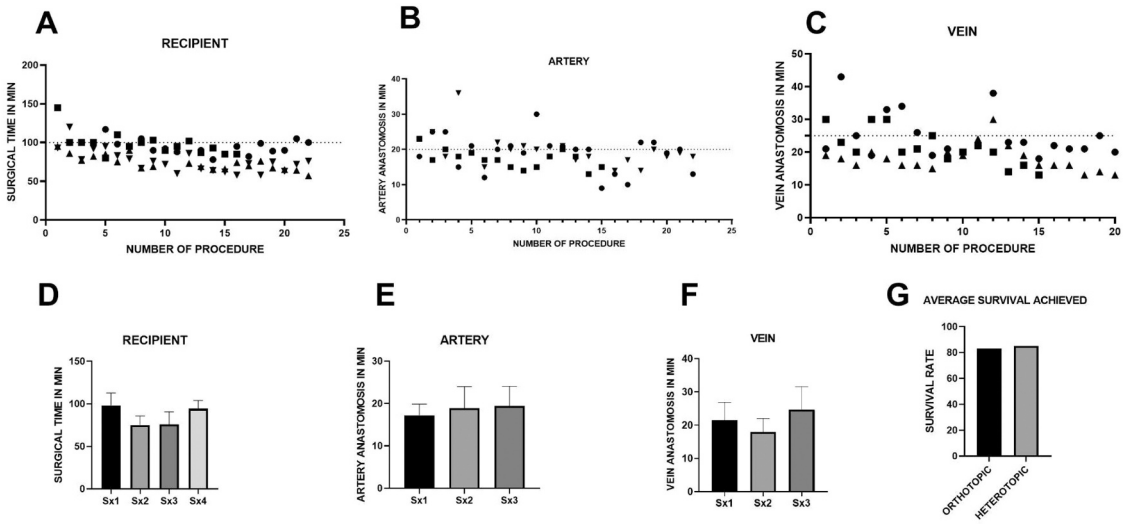

Fig. 6. The learning curves for the recipient surgery (A), the artery anastomosis (B), the vein anastomosis (C). Each point represents a different procedure and each shape a different surgeon (Sx). And the average time of each Sx for performing the recipient surgery (D) the vein anastomosis (E), the artery anastomosis (F) and the average time for the recipient differentiating between the orthotopic and heterotopic models (G).

orientation and ensuring anastomosis stability are also key issues that can impact graft survival. Moreover, the high level of precision required in revascularizing and reconnecting the gut makes the procedure technically demanding, with significant variability in outcomes depending on the surgeon's skill and experience. Reports indicate that complications such as anastomotic failure, graft ischemia, and vascular thrombosis occur frequently [9]. It is essential to complete these anastomoses within 40 minutes to minimize warm ischemia time, which can negatively impact post-surgical outcomes [24]. Our team uses 9–0 nylon monofilament for anastomoses, in line with most reported studies, though some research groups use 7–0 or 10–0 monofilament. There is no consensus on the optimal suture size, and we believe the choice depends on the surgeon's preference and comfort [7–9,13,24].

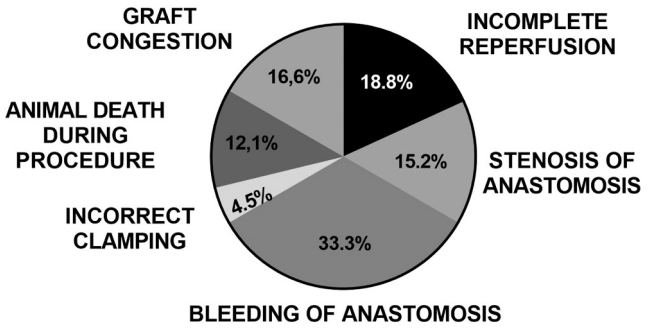

Fig. 7. The complications reported by the surgeons.

Post-surgical care is also crucial for ensuring the well-being of the animals and obtaining reliable results. We conduct at least two daily observations of the recipients, promptly addressing any signs of pain or distress. In heterotopic ITx, where the graft is exteriorized through ostomies, there is a risk of self-mutilation. However, through diligent monitoring and appropriate analgesic treatment, we have reduced graft loss due to this issue to less than 3 % in our heterotopic ITx cases. This indicates that such complications should not deter the use of heterotopic ITx models in research.

Our experience demonstrates that with systematic training, careful attention to donor surgery, graft preservation, and vascular anastomosis techniques, successful ITx procedures can be consistently achieved. Key factors such as minimizing donor surgery time, reducing cold ischemia, and performing precise anastomoses are critical for success. Additionally, proper post-surgical care ensures recipient well-being, further supporting the validity of these models. This manuscript serves as a guide for other research groups interested in developing ITx models and emphasizes the value of proper animal handling, microsurgical technique training, and continuous improvement of transplantation procedures to enhance outcomes in experimental transplantation models offering valuable insights into microsurgical techniques and best practices that can be applied to a range of experimental transplantation studies.

Conclusion

Many research groups have successfully developed experimental ITx models in rats, providing valuable insights into the procedures and techniques required to achieve successful outcomes [7,25]. This study outlines the key steps necessary to establish and standardize ITx models, from initial microsurgical training to protocol development aimed at ensuring prolonged graft and recipient survival.

Establishing dedicated microsurgery teams is essential for advancing both basic and translational research. With consistent training, experience, and case volume, achieving reproducible results becomes feasible, enabling the development of robust experimental ITx models that are critical for improving transplantation outcomes.

In this study, we successfully established a reproducible and reliable ITx model, demonstrating its effectiveness in addressing key challenges such as graft rejection, immune tolerance, and immunosuppressive strategies. Our protocol serves as a comprehensive and validated framework that can guide other research teams in developing similar models. By adopting and building upon our methodology, laboratories can accelerate their research efforts, ensure consistency in experimental designs, and contribute to optimizing intestinal transplantation strategies. The continued refinement and widespread adoption of standardized ITx models like ours will be instrumental in driving innovation, improving patient outcomes, and shaping the future of transplantation research.

Patient consent

Not applicable

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used AI in order to check grammar and improve readability given that English is not their native language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of this publication.

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CRediT authorship contribution statement

J. Azpiroz: Primary experimental data set used, collected and statisticaly analized the data and wrote the original draft and edited the following versions. **J.C. Abate:** Provided data and then was the main collaborator during the edition process. **A.M. Andres:**

Provided data. **J.E. Moreira:** Provided data. **F. Hernandez Oliveros:** Directed one of the authors in the training process and helped edit the manuscript. **G. Gondolesi:** Directed one of the authors and helped edit the mauscript. **N.R. Lausada:** Developed the original method and personally trained all the surgeons, directed some of the authors and helped edit the manuscript. **P. Stringa:** Directed and trained all the authors, helped write and correct the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Gabriel E. Gondolesi, MD- editor of Intestinal Failure If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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