STUDY PROTOCOL

“Morbidity of Conventional and No-touch Saphenectomy in Coronary Artery Bypass Grafting, a Randomized Non-inferiority Clinical Trial”

MD. Juan Andrés Montero
CI: 4.823.882-3
Cel: 099428604
Address: Scoseria 2672, Montevideo, Uruguay.
Email: juani.montero94@gmail.com
Instituto Nacional de Cirugía Cardíaca.
July 5th, 2024.

Summary:

A clinical research project will be carried out, it consists of a non-inferiority study. The objective is to compare the morbidity of two different surgical techniques for the extraction of the internal saphenous vein, intended to be used as a conduit in coronary bypass.

Current clinical trials have shown that the no-touch saphenectomy technique has had a positive impact on the short- and long-term patency of coronary bypass, compared to the conventional extraction technique. It is important to highlight that the conventional technique is the most used in our country (Uruguay, South America), while the "no touch" has fallen into disuse.

Given this disparity in the application of the techniques, it is considered essential to compare both methods in terms of morbidity. For this purpose, a prospective randomized clinical trial will be carried out. The primary objective will be to investigate the non-inferiority of the "no touch" technique compared to the conventional technique, specifically focusing on postoperative morbidity of the surgical site. This morbidity will be defined and measured in terms of local infection, hematoma, flictenes, secretions, necrosis, wound dehiscence, paresthesias, pain and functional impotence.

Introduction:

The internal saphenous vein, as an inverted free graft, has been one of the most commonly used conduits to perform coronary bypass in myocardial revascularization surgery since 1967. Over the years, various dissection techniques for this vein have been described, which include the conventional one with continuous or sectional incisions, the "no touch" and the endoscopic route.

The patency of the venous conducts tends to decrease significantly over time. One year after surgery, around 10% of venous bypasses are occluded; the occlusion rate increases 1% to 2% annually over the next 1 to 6 years, and increases 4% annually for 6 to 10 years postoperatively. Ten years after surgery, up to approximately 50% of vein grafts are occluded.

On several occasions, research has been carried out on the factors that influence the patency of these grafts, such as the quality and run-off of the native vessels, the harvesting technique and the patient's risk factors.

Currently, the most widely used technique remains the conventional one, which involves a continuous incision in the skin of the leg or thigh. In this technique, a dissection of the subcutaneous tissue surrounding the vein is performed, the collaterals are ligated, and the free venous duct is sectioned. The length of the conduit varies depending on the amount of bypass to be performed.

The "no touch" technique, proposed by Domingos S.R. Souza in 1996, despite having demonstrated superiority in bypass patency according to several studies, it is not the most commonly used nowadays. A randomized controlled trial showed better graft patency in the short and medium term, as well as less intimal hyperplasia when using the "no touch" technique compared to conventional extraction. From a technical point of view, this methodology implies avoiding all direct contact with the venous duct. The vein is removed with perivascular tissue acting as protection against manipulation-induced damage, thus preserving endothelial nitric oxide synthase activity. This results in effective protection against vasospasm, eliminating the need for overdistention. The adventitia and structures within the surrounding tissue pedicle possess mechanical and functional properties that protect against spasm and ischemia, while preventing the phenomenon known as kinkin. Despite these demonstrated advantages, the "no touch" technique faces limited adoption compared to conventional vein stripping in coronary bypass surgery.

There are not many relevant randomized clinical trials that compare the morbidity of this technique with the conventional one. In this context, we consider it crucial to evaluate whether there are significant differences in terms of wound morbidity in the mid-postoperative period (1 week), late (1 month) and long-term postoperative period (6 months).

We will define each variable previously: it will be considered to have a local infection when the wound shows signs of flow and it has been necessary to start antibiotic treatment, hematoma when there is a tumor or abnormal hardening caused

by the accumulation of blood, flictenes when a skin blister appears on the wound that contains watery substances and not pus, secretions when the wound secretes a liquid (serous, bloody, purulent), necrosis when there is a necrotic plaque in the wound larger than 10 x 10 mm, dehiscence of the wound when the suture loses continuity, paresthesia when there is a tingling sensation due to an irritative sensitivity disorder, pain when it is located at the level of the wound and functional impotence when it prevents or limits ambulation.

Revision:

According to current literature, patency at 16 years of venous bypass using the conventional technique is 64%, compared to 83% achieved with the "no touch" technique. This last index even resembles the Gold-standard represented by the internal mammary artery. Although it has been shown that the "no touch" technique preserves numerous properties of the vein, favoring a longer duration of its patency, the conventional technique continues to be the preferred one in clinical practice. This technique is recognized as a Class IIa recommendation in the 2018 European Society of Cardiology and European Association for Cardiothoracic Surgery myocardial revascularization guidelines.

Existing studies have focused their attention on evaluating the patency of the ducts; however, there is a lack of solid information on the morbidity associated with this technique in the lower limb of patients. During the extraction of the saphenous vein using the "no touch" technique, it is sectioned with the perivascular adipose tissue and the saphenous nerve of the leg, therefore, it is of great interest for us to evaluate the incidence of the postoperative complications, previously mentioned, and compare these results with those obtained through the conventional technique.

A single-center randomized clinical trial was published in 2014, in Canada, carried out by Domingos S.R. Souza and Stephen E. Fremes. This study demonstrated significant differences in leg morbidity at 3 months, favoring the conventional technique, although this difference did not persist at one year. An important limitation was the small number of participants, with only 17 patients. In order to overcome this limitation, we intend to carry out a study with a larger sample of patients.

In 2021, another multicenter randomized clinical trial was published in China, led by Shengshou Hu, which included a considerable number of patients, 2,638 in total. This study not only compared patency at 1 year, but also wound morbidity. Significant differences between both techniques were identified before hospital discharge, such as an increase in exudate, numbness and edema in patients undergoing the "no touch" technique, but the difference was not maintained after one year. It is relevant to note that no serious complications, such as necrosis or compartment syndrome, were recorded in any of the patients. Regarding pain rates, no significant differences were observed at three months or one year. Furthermore, multivariate analysis revealed that female sex, diabetes, and hypertension were independent predictors of wound complications. These findings provide valuable information for understanding the long-term results of both techniques.

Objectives:

Our primary objective will be to demonstrate the non-inferiority of the "no touch" technique over the conventional technique in terms of wound morbidity in patients undergoing coronary revascularization, within a non-inferiority margin. Defining morbidity as the combined result of local infection, hematoma, blisters, secretions, necrosis, wound dehiscence, paresthesias, pain and functional impotence.

We sought to achieve as a specific objective the incidence of each of the study factors: local infection, hematoma, blisters, secretions, necrosis, wound dehiscence, paresthesias, pain, functional impotence and then compare them between both groups at different times.

The anatomopathological study of some of the saphenous vein preparations, one “no touch” and the other conventional, will also be carried out using optical microscopy and ultrastructural comparisons using transmission electron microscopy.

Additionally, patients will be offered computed tomography angiography every year to evaluate graft patency.

Through multivariate analysis, the relationship with independent factors will be analyzed.

Null hypothesis: "no touch" saphenectomy is inferior to the conventional technique.

Alternative hypothesis: "no touch" saphenectomy is not inferior to the conventional technique.

Methodology:

The design corresponds to a single-center, open, non-inferiority, controlled, randomized clinical trial. The trial will be blind for the patient and to the investigator that will evaluate the morbidities in the postoperative time, only the surgeon knows which technique is used.

The target population will be those over 18 and under 70 years of age, undergoing coordination coronary revascularization surgery, in which it is necessary to use the internal saphenous vein as a conduit. Those who do not meet the entry criteria, emergency surgeries, patients with poor metabolic control (HbA1c > 6.5%), chronic venous insufficiency or chronic obstructive arteriopathy of the lower limbs, and type II obesity (BMI>35) will be excluded.

Given that the number of patients assigned to each group is required to be similar throughout the study, the randomization method that we believe is most appropriate is assignment through permuted block randomization of four.

Evaluations will be carried out in person before discharge from the hospital, approximately one week after the operation. Subsequently, in-person assessments will be conducted at the one-month follow-up, and finally, telephone assessments will be conducted at six months. The assessment will be carried out by researchers who are blind to the randomization group and will record on a form, indicating the presence (1) or absence (0) of the following aspects: local infection requiring antibiotics, hematoma, blisters, secretions, necrosis and dehiscence of the wound. . As for the rest of the variables, such as paresthesias, pain and functional impotence, they will be recorded according to the pain scale from 0 to 10.

The data of each patient will be grouped into tables, including relevant personal history and answers to the questionnaires. The analysis will then be carried out from these forms using the corresponding analytical tests.

A monitoring and safety committee will be appointed that will continuously evaluate adverse effects (included in the primary objective) as well as clinical results (operative and 1-year mortality) and will consider suspension of the study in the event of a significant increase.

Sample calculation:

A probability of complication of saphenectomy by conventional or “control” technique of 10% was assumed, based on studies from our institution, and according to preliminary studies we expect to find 50% more in the "no touch" technique, therefore 15%. To determine the non-inferiority margin, 10 patients who were recently revascularized, 5 men and 5 women, were asked how many times more pain or local infection they were willing to accept with the “no touch” technique in exchange for greater bypass patency. short and long term. When analyzing the results, it is obtained that they would be willing to accept up to twice as many complications by applying the "no touch" technique, therefore the non-inferiority limit will be 20%. With these values, assuming a 95% confidence interval and a power (1 - beta) of 80%, and taking into account a probable 20% of lost patients, we can calculate the necessary population sample size, which was in total 52 patients; 26 people in the group with conventional technique and 26 in the “no touch”.

Informed consent:

Two informed consents have been prepared that cover details about the research, its duration and relevance, the procedure to be performed, as well as the associated risks and benefits. In preoperative evaluations, the surgical team personnel will be responsible for obtaining this consent. In this document, the patient will have the opportunity to express their willingness to participate or not in the research.

Institution:

The study will be carried out at the Instituto Nacional de Cirugía Cardíaca, a medical care institution dedicated to the diagnosis and treatment of cardiovascular conditions, the first institute of cardiac surgery and hemodynamics in the country with more than 50 years of experience. Located at the address Luis A. de Herrera 2275, SMI Hospital, telephone +598 2481 0209, email cirugia@incc.com.uy.

Schedule:

The schedule consists of a first stage where the surgeries of the 52 patients will be performed, we estimate 9 months. The second stage will be data collection, 3 controls will be carried out: 7 days after surgery, in the polyclinic approximately one month later, and 6 months later by phone call.

After one year, a coronary CT angiography will be performed to evaluate the patency of the bypasses. The data will be grouped into tables by the team of researchers. The duration of the first stage will be from the first surgery to the last, we estimate that it will be 6 months.

The second stage, data collection, will begin simultaneously with the first, and will end 12 months after the last surgery.

The third stage will be the processing, tabulation and interpretation of the data, which will be done in 1 month.

The fourth stage is the publication of the results.

The authors declare the absence of conflicts of interest.

Bibliography:

1. Dashwood, M. R., Pinheiro, B. B., & Souza, D. S. R. (2022). Impact of saphenous vein harvesting on graft diameter: Supporting the no-touch technique. In JTCVS Techniques (Vol. 16, pp. 105–106). Elsevier Inc. https://doi.org/10.1016/j.xjtc.2022.08.011
2. Deb, S., Singh, S. K., de Souza, D., Chu, M. W. A., Whitlock, R., Meyer, S. R., Verma, S., Jeppsson, A., Al-Saleh, A., Brady, K., Rao-Melacini, P., Belley-Cote, E. P., Tam, D. Y., Devereaux, P. J., Novick, R. J., & Fremes, S. E. (2019). SUPERIOR SVG: No touch saphenous harvesting to improve patency following coronary bypass grafting (a multi-Centre randomized control trial, NCT01047449). Journal of Cardiothoracic Surgery, 14(1). https://doi.org/10.1186/s13019-019-0887-x
3. Gaudino, M., Antoniades, C., Benedetto, U., Deb, S., di Franco, A., di Giammarco, G., Fremes, S., Glineur, D., Grau, J., He, G. W., Marinelli, D., Ohmes, L. B., Patrono, C., Puskas, J., Tranbaugh, R., Girardi, L. N., & Taggart, D. P. (2017). Mechanisms, consequences, and prevention of coronary graft failure. Circulation, 136(18), 1749–1764. https://doi.org/10.1161/CIRCULATIONAHA.117.027597
4. Inaba, Y., Yamazaki, M., Ohono, M., Yamashita, K., Izumida, H., Hayashi, K., Takahashi, T., Kimura, N., Ito, T., & Shimizu, H. (2020). No-touch saphenous vein graft harvesting technique for coronary artery bypass grafting. General Thoracic and Cardiovascular Surgery, 68(3), 248–253. https://doi.org/10.1007/s11748-019-01186-4
5. Kopjar, T., & Dashwood, M. R. (2016). Endoscopic versus "no touch" saphenous vein harvesting for coronary artery bypass grafting. In Angiology (Vol. 67, Issue 2, pp. 121–132). SAGE Publications Inc. https://doi.org/10.1177/0003319715584126
6. Pettersen, Ø., Haram, P. M., Winnerkvist, A., Karevold, A., Wahba, A., Stenvik, M., Wiseth, R., Hegbom, K., & Nordhaug, D. O. (2017). Pedicled Vein Grafts in Coronary Surgery: Perioperative Data From a Randomized Trial. Annals of Thoracic Surgery, 104(4), 1313–1317. https://doi.org/10.1016/j.athoracsur.2017.03.076
7. Ragnarsson, S., Janiec, M., Modrau, I. S., Dreifaldt, M., Ericsson, A., Holmgren, A., Hultkvist, H., Jeppsson, A., Sartipy, U., Ternström, L., Per Vikholm, M. D., de Souza, D., James, S., & Thelin, S. (2020). No-touch saphenous vein grafts in coronary artery surgery (SWEDEGRAFT): Rationale and design of a multicenter, prospective, registry-based randomized clinical trial. American Heart Journal, 224, 17–24. https://doi.org/10.1016/j.ahj.2020.03.009
8. Samano, N., Geijer, H., Liden, M., Fremes, S., Bodin, L., & Souza, D. (2015). The no-touch saphenous vein for coronary artery bypass grafting maintains a patency, after 16 years, comparable to the left internal thoracic artery: A randomized trial. Journal of Thoracic and Cardiovascular Surgery, 150(4), 880–888. https://doi.org/10.1016/j.jtcvs.2015.07.027

9. Souza, D. S. R., Christofferson, R. H. B., Bomfim, V., & Filbey, D. (1999). "no touch" technique using saphenous vein harvested with its surrounding tissue for coronary artery bypass grafting maintains an intact endothelium. Scandinavian Cardiovascular Journal, 33(6), 323–329. https://doi.org/10.1080/14017439950141362
10. Souza, D. S. R., Dashwood, M. R., Tsui, J. C. S., Filbey, D., Bodin, L., Johansson, B., & Borowiec, J. (2002). Improved Patency in Vein Grafts Harvested With Surrounding Tissue: Results of a Randomized Study Using Three Harvesting Techniques.
11. Souza, D. S. R., Arbeus, M., Botelho Pinheiro, B., & Filbey, D. (2009). The no-touch technique of harvesting the saphenous vein for coronary artery bypass grafting surgery. Multimedia Manual of Cardio-Thoracic Surgery, 2009(0731). https://doi.org/10.1510/mmcts.2008.003624
12. Tian, M., Wang, X., Sun, H., Feng, W., Song, Y., Lu, F., Wang, L., Wang, Y., Xu, B., Wang, H., Liu, S., Liu, Z., Chen, Y., Miao, Q., Su, P., Yang, Y., Guo, S., Lu, B., Sun, Z., … Hu, S. (2021). No-Touch Versus Conventional Vein Harvesting Techniques at 12 Months After Coronary Artery Bypass Grafting Surgery: Multicenter Randomized, Controlled Trial. Circulation, 144(14), 1120–1129. https://doi.org/10.1161/CIRCULATIONAHA.121.055525
13. Tsuneyoshi, H., Setozaki, S., Katayama, H., Wada, T., Shimomura, S., Takeuchi, A., Sugaya, A., & Komiya, T. (2022). Early and Midterm Outcomes of "no touch" Saphenous Vein Grafts in Japanese Institutions. Brazilian Journal of Cardiovascular Surgery, 37(Special Issue 1), 42–48. https://doi.org/10.21470/1678-9741-2022-0121
14. Verma, S., Lovren, F., Pan, Y., Yanagawa, B., Deb, S., Karkhanis, R., Quan, A., Teoh, H., Feder-elituv, R., Moussa, F., Souza, D. S. R., & Fremes, S. E. (2014). Pedicled no-touch saphenous vein graft harvest limits vascular smooth muscle cell activation: The PATENT saphenous vein graft study. European Journal of Cardio-Thoracic Surgery, 45(4), 717–725. https://doi.org/10.1093/ejcts/ezt560
15. Weiss, M. G., Nielsen, P. H., James, S., Thelin, S., & Modrau, I. S. (2023). Clinical Outcomes After Surgical Revascularization Using No-Touch Versus Conventional Saphenous Vein Grafts: Mid-Term Follow-Up of Propensity Score Matched Cohorts. Seminars in Thoracic and Cardiovascular Surgery, 35(2), 228–236. https://doi.org/10.1053/j.semtcvs.2021.12.002.
16. Sealed Envelope Ltd. 2012. Power calculator for binary outcome non-inferiority trial. [Online] Available from: https://www.sealedenvelope.com/power/binary-noninferior/ [Accessed Tue Jan 02 2024].