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SHORT COMMUNICATION

Technical Approach to Local Therapy in Ischemic Stroke

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ABSTRACT

Local therapy is an increasingly achievable alternative for neurological diseases such as stroke. For its use to be a reality, it is still necessary to develop techniques that facilitate its administration and maximize its effect. In this short communication, we present a technique of intracerebral therapy administration. This procedure requires the use a navigation-guided stereotactic surgical technique to inject the treatment into the therapeutic target, even in areas that are difficult to access or extremely large. Such a method is not only fast and feasible, but it can be a standardized technique for multicentre clinical trials.

Keywords: Local therapy, Stroke, Intracerebral administration route

1 Introduction

The treatment of stroke continues to be one of the greatest challenges of the 21st century, with a high incidence and great socio-economic budget. The sequelae of stroke are frequently permanent but pharmacological treatments fail to reverse the functional losses caused by stroke.

It is possible that one of the causes of failure of current treatments is the difficulty of treating brain lesions locally, reducing the effectiveness of any treatment administered. Being so, the route of administration at the brain level constitutes one of the great challenges in the search for neuro-restorative treatments in stroke, since each route offers great benefits, as well as limitations [1]. Among the routes used, the intra-arterial route, the intravenous route, the intraparenchymal route and the intraventricular route stand out [1].

Focusing on the intracerebral route, its greatest advantage is the possibility of implanting the entire dose in the therapeutic target, thus optimizing treatment. However, the disadvantage is the invasive nature of the intervention.

In this communication, we present a form of rapid and safe implantation that allows covering extensive and deep infarcted areas. Furthermore, due to the versality of the procedure, it is not only possible to administer fluids, but also other innovative therapies such as cell therapy or biomaterial vehicles with different degrees of viscosity that cannot be administered parenterally or intravenously. arterial.

This procedure can be performed under local anesthesia and mild sedation. This is the same technique used in routine practice to perform neuronavigation-guided brain biopsies [2]. This procedure stands out for its precision and its usual use, thus achieving standardization of the technique, a fundamental aspect in multicenter clinical trials.

This procedure has been used in the CELICTUS clinical trial (EC10-069), carried out at the San Carlos Clinical Hospital. It is a randomized, blinded and controlled phase IIa clinical trial. The

objective of this clinical trial is to verify feasibility and safety of allogeneic mesenchymal stem cells derived from fatty tissue in stroke patients. This study has been approved by the Ethic Committee of the Hospital Clínico San Carlos (EC-INC 09/01 - N.E. 2011-001393-26 - C.I. 11/279) and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The objective of the current communication, therefore, is to present a form of stem cell implantation in a stroke patient using a stereotaxic technique.

2 Materials and Methods

The intracranial cell implantation procedure consists of the steps listed below.

2.1 Treatment

Our research team has used mesenchymal stem cells derived from fatty tissue generated upon request by Histocell S.L. These cells are obtained through abdominal liposuction from donors who met the requirements of current regulations. Cells should be isolated and processed under conditions of GMP (good manufacturing practice) to guarantee maximum sterility during their production. Once the tissue is processed, they are expanded in cell culture. DMEN F12 media and fetal bovine serum (FBS) are used for its maintenance. When cells reach the confluence, it initiates the first pass. The cells used do not exceed passage 7 to ensure that the number of divisions is less than 50. Finally, cells require to be packaged according to the legislation in force until the time of their implantation in the operating room.)

This method is valid for isolating mesenchymal stem cells, but the protocol for obtaining them varies according to the source of origin. Bone marrow or peripheral blood, for example, have other compounds so the procedure, although it shares some steps, differs in the enzymes used or in the centrifugation times, among other details.

2.2 Planning

The first step consists of obtaining a brain resonance imaging scan (MRI) of 1 mm thin sections in three dimensions (3D). This makes possible to generate a 3D image of the cranial content and, therefore, obtain a 3D image of the infarcted brain tissue volume and its relation to healthy tissue. In this way, the next step is to determine the implantation areas and verify that the trajectories are safe, avoiding damaging blood vessels or potentially eloquent areas (Figure 1).

Once the targets of interest and the implantation trajectories are identified, preoperative planning is performed following the same process as for a neuronavigation-guided brain biopsy using a Medtronic® StealthStation S7 Surgical Navigation System.

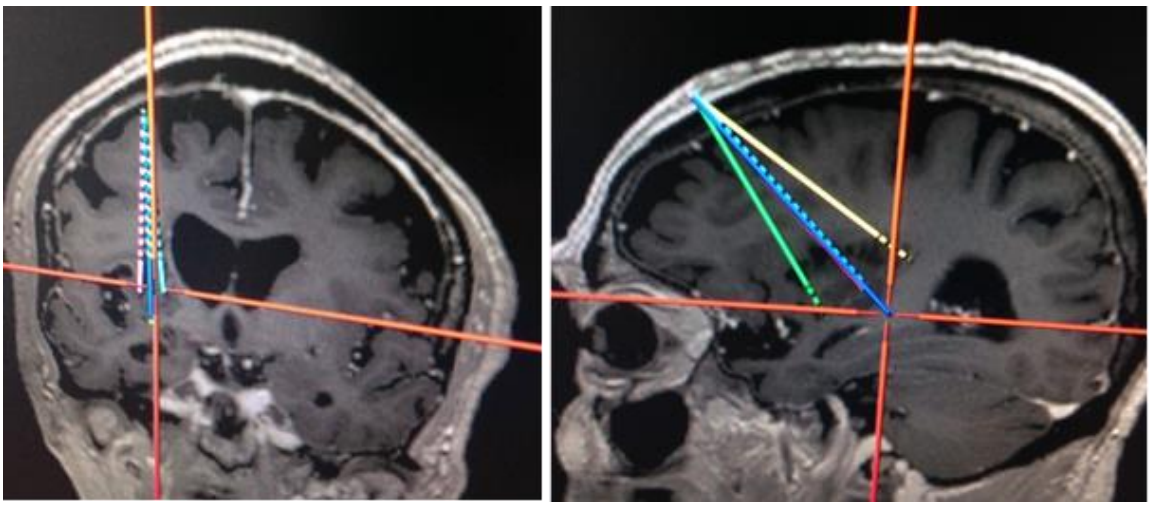

Figure 1: *Peri-infarct and central planned trajectories in the lesion.*

A relevant question is the number of targets and, therefore, of trajectories to be carried out. This question is currently undefined [3-6]. The rule chosen to determine the number of surgical targets may be "as many targets as required to encompass a greater volume of healthy brain tissue in the periphery of the stroke". The reason is that the chosen targets can constitute the tissue that supplies the functions of the damaged tissue and, therefore, those that we intend to enhance with the treatment [7-8]. In our experience, we recommend a 5-trajectory planning: anterior, posterior, medial lateral and central (superior and inferior), taking as reference a specific point of the ischemic volume

2.3 Surgery Procedure

The surgery is performed under local anesthesia and mild sedation, preferably without muscle relaxants (to allow neurological assessment during each of the journeys), frameless with the head fixed in Mayfield® and in a supine position. The Navigus Medtronic ® Stereotaxic Brain Biopsy System Optical Neuronavigation System is recommended. It is important to emphasize the use of the optical system, since the hollow cannula of the system will allow us to infuse cells. Once a single burr hole is made, which reduces surgical time and risk (Figure 2). Next, the anchoring system of the system screwed to the skull is placed, the stem is placed inside it and fixed with the thread.

Figure 2: *Picture of the trephine made in the skull of the patient. The location of the trephine is defined by the location of the stroke.*

When placing the system, it must bear in mind that the structure is limited by a certain degree of angulation (15-20º), so the location of the trephine is essential to ensure complete coverage of the infarcted area, especially in those volumes very extensive ischemic.

The biopsy needle is hollow inside (as this is where it is aspirated to extract brain tissue samples); however, it will be use to introduce the cells in question. The needle of the system is navigable and avoids the placement of the stylet inside it, which would cause a loss of cells (Figure 3).

Figure 3: *Navigus Medtronic Brain Biopsy Cannula. (At the tip, fenestration through which the cells finally emerge).*

Depending on the therapeutic objective and the type of medication, the administration guidelines should be considered. For example, administering a total volume of 1 ml of treatment, it could be distributed in 5 paths of 0.2 ml each. The dose for each path could then be distributed to different parts along the path. This type of dosage would be adapted to 1) the therapeutic objective of distributing the medicinal product in the greatest number of possible targets close to the injury, thus improving its global effect, 2) to the tissue characteristics.

Although there is no consensus on the appropriate dose, in the case of cells, we suggest a total dose of 10 million in a volume of 1 mL. The dose should be distributed in 5 trajectories of 0.2 mL each (that is 2 million cells per trajectory) [3, 5,6]. In each trajectory, the total volume is divided into 10 injections, previously scheduled at strategic points along the trajectory. In each injection, 0.02mL (= 200,000 cells) was administered.)

The administrations are carried out in the following coordinates: anterior, posterior, medial, lateral and central (superior and inferior), all located in the zone of healthy tissue-infarct transition (periphery).

It is also required an insulin syringe filled with 1mL of the cell treatment, not with saline or similar. Once the cannula is loaded with the cell preparation, it should be located into the brain tissue under the usual technique of guided brain biopsy with neuronavigation. When the target is reached, the insulin syringe containing 1mL of the cell preparation is connected at the back of the cannula, and a progressive ascent of the 2mm cannula is carried out injecting 0.02 ml in each ascent up to a total of 10 ascent-injections (20mm of path = 0.2 ml of infused treatment). The progressive ascent-injection allowed us to administer the cells in a single path but not in a single point. At the end of the course, the cannula is removed while confirming that there is no obstruction of the cannula and the next course is made (Figure 4). In our experience, this is the only way to ensure that the administered dose is correct and exact. Simultaneously, this procedure avoids contamination that any other external substance can generate.

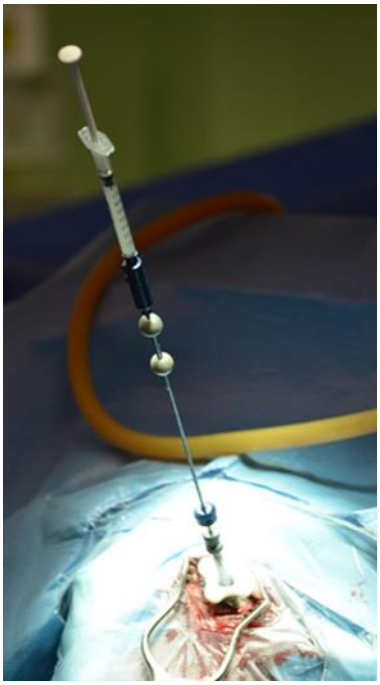

Figure 4: *Brain biopsy cannula placed in trephine and insulin syringe connected to cannula containing stem cells. The cannula is pre-filled with cells to guarantee the dose.*

Throughout the procedure, motor and language skills are evaluated by a neurologist. The assessment included standard neurological test during surgery as reading, word repetition, meet orders and color naming, and moving upper and lower contralateral limbs, flexion, extension and fine movements of the hand. In case a frank neurological deterioration is observed, the intervention should be stopped. In addition, a brain computed tomography (CT) is performed immediately after the end of the surgery, to rule out bleeding and confirm trajectories.

3 Conclusions

We can conclude that the implantation of intracerebral cell therapy is feasible under the stereotaxic technique guided by optical neuronavigation. It is a high precision procedure, capable of planning and depositing the treatment of interest in any area of the brain parenchyma, even in deep areas with difficult access or extremely large areas.

4 Declarations

4.1 Study Limitations

Possible risks derived from this procedure include risks of intracranial bleeding, difficulty in administering medication due to the volume of the injury. Specifically, regarding the stroke condition, among the limitations we could mention,

i) the time of evolution of the stroke: this technique has been carried out in patients who had suffered chronic heart attacks of long evolution, all of more than one year, where the neurological deficit was already established. No improvement had been observed after multiple rehabilitative treatments.

ii) The volume to be implanted is limited by the brain tissue, since high volumes could generate intracranial hypertension, therefore the dose is also limited.

iii) The size of the infarct is also a technical limitation, since its extension makes it difficult to carry out the trajectories: in addition, it cannot be established whether larger strokes would require a

higher dose and more implantation routes.

iv) The possibility of performing several treatment sessions given the invasiveness of the technique.

In addition, there is the risk of rejection of the implanted material and, ultimately, that this material is the origin of a tumor reaction. Regarding the design, maintaining the double-blind condition is difficult to maintain when working on brain surgery since placebo surgeries are not ethically acceptable.

4.2 Warning for Hazard

In order to guarantee the sterility of cell production, as well as its proper handling according to current regulations, the cells used have been processed under GMP (good manufacturing practice) conditions. In addition, for its correct homogenization it was necessary to use an excipient authorized by the AEMPS (Spanish Agency for Clinical Trials). In our case we have chosen Hypo Thermosol, whose main component is Dextran-40, which is a solution used to expand the plasma volume. HypoThermosol solution is in compliance with USP <71 & gt; Sterility and USP <85 & gt; of Endotoxins, and is produced in accordance with cGMP standards.

Regarding surgery hazards, it is remarkable the added difficulty in cell implantation for those cases in which the stroke lesion is particularly extensive.

4.3 Acknowledgments

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4.4 Funding Source

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4.5 Ethical Approval

This study has been approved by the Ethic Committee of the Hospital Clínico San Carlos (EC-INC 09/01 - N.E. 2011-001393-26 - C.I. 11/279) and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

4.6 Informed Consent

Informed consent has been taken from the patient by adhering to ethical standard in research.

4.7 Competing Interests

The authors have declared that no competing interests exist.

How to Cite this Article:

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