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Sponsor:
Centro Cardiologico Monzino, [redacted]

Title of Protocol:

MIGRAINE IN PATIENTS WITH PATENT FORAMEN OVALE: IDENTIFICATION OF A RISK PROFILE FOR THE DEVELOPMENT OF AURA AND CEREBRAL ISCHEMIC EVENTS. The LEARNER Study

Site:
Centro Cardiologico Monzino, Istituto di Ricovero e Cura a Carattere Scientifico, S.p.A.

Comitato Etico del Centro Cardiologico Monzino

Principal Investigators:
[redacted]

Versione n° 01 Data 00.00.0000

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0. Investigator Agreement

I declare that I have read and approved the protocol set out in this document.

I am aware of the responsibility to be assumed as an investigator in accordance with the provisions of the rules of Good Clinical Practice, the Declaration of Helsinki, and the study protocol and I undertake to conduct the study according to the aforementioned directives and to direct and assist the study staff assigned by me.

Principal Investigator:

Sign _____ Date: _____

1. General information

Title: MIGRAINE IN PATIENTS WITH PATENT FORAMEN OVALE: IDENTIFICATION OF A RISK PROFILE FOR THE DEVELOPMENT OF AURA AND CEREBRAL ISCHEMIC EVENTS. The LEARNER Study

Version number: 01
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Sponsor: [redacted]

Principal investigator:

[redacted]

Co-Investigators

[redacted]

2. Background and rational

Background

Migraine is a primary disorder of multifactorial etiology [1] with a prevalence in the United States of 28 million people (13%) which result in affected with a consequent economic burden on the health system.

Numerous studies have documented a significant association between migraine, especially migraine with aura, and the presence of perviety of the oval foramen[8].

Symptomatic patients for migraine with aura have a higher prevalence of PFO than migraines without aura and patients who do not suffer from migraine [4] and have a 4.5 times higher probability of encountering a 50% reduction in the frequency of migraine attacks after PFO closure compared to symptomatic subjects for migraine without aura [7].

The oval foramen remains pervious after birth in about 20% of the population and predominantly in female subjects. Closure of the oval foramen pervio (PFO) resulted in a partial or complete regression of migraine symptomatology in several retrospective and monocentric[studies 4–6]. In these studies, percutaneous correction of PFO had been performed for the secondary prevention of stroke [4] or for the presence of conditions related to intracardiac shunt such as decompression sickness in divers [6]. Since there are no diagnostic or provocative tests capable of correlating PFO to migraine, it is difficult to understand which patients will be responsive to the elimination of the right-left intracardiac shunt after correction of PFO.

Other possible clinical benefits of PFO closure include reducing the sequalities of a paradoxical embolism such as ischemic stroke, myocardial infarction[11, 12] and cognitive impairment.

Although it has not been documented, the prevention of chronic headache through the correction of PFO in the earliest and phase phase of the disease can also be beneficial. Current estimates indicate that 4% of the general population suffers from chronic migraine [13] which in 75% of cases is the result of a transformation from a phasic or periodic migraine. [14]. Eradication of the source of migraine can also be positive against these progressive pathological processes. However, to date, international guidelines (ESC and AHA/ACC) do not include migraine among the indications to the correction of PFO.

he prevalence of PFO in subjects with migraine with aura varies between 41% and 89%[4] , while it is between 7% and 34% in symptomatic patients for migraineswithout aura and between 20% and 25% in controls without migraine [4] .

This association is two-way because the risk of developing a neurological ischemic event in a subject with PFO and migraine is 5.1 times higher (95% CI, 4.67 -5.59) than in a subject without PFO [9] and young women are more frequently symptomatic for migraine when affected by PFO.

In women and patients with stable coronary artery disease, in antiplatelet therapy with aspirin, high platelet reactivity (HAPR) or resistance to aspirin has been described, which is associated with unfavorable clinical outcomes. A study conducted by Jesurum et al, suggested that subjects with migraine have a higher prevalence of HAPR than healthy subjects or patients with stable coronary artery disease being treated with aspirin 325 mg. However, the clinical implications of HAPR in subjects with emicrania and PFO require further investigation of analysis for the high risk of cerebral stroke and myocardial infarction and highlight the need to prescribe preventive antiplatelet therapy early.

In addition, the extent of the right-left shunt as assessed and measured at the transcranial Doppler also increases progressively from the migraine-free control groups, to the migraineranics without aura and in those with aura [17] .
Recent studies have shown that a prominent Eustachian valve and a Chiari network, as an embryonic residue in the right atrium, are more often detectable in migraine patients with aura (100% in migraine with aura vs 55% in non-migraines)[19.20] and this could explain the increase in dx-sin shunt. In addition, an analysis of the anatomy of the interatrial septal (SIA) showed the presence of SIA aneurysm in 13% of patients with migraine compared to 1.9% of control subjects (p=0.05)[21]. In addition, among migraine patients, SIA aneurysm was predominantly observed in subjects with aura (28%) compared to those without aura (3.6%) [21].

Rational

The premium (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management) study hypothesis was based on the possible significant reduction in the frequency of migraine attacks with and without aura after percutaneous correction of PFO and broad dx-sin shunt in patients symptomatic for migraine from 6 to 14 days/month and not responsive to drug therapies.
The primary endpoint of the studywas to reduce the frequency of migraine attacks (with or without aura) by at least 50%; the proportion of patients with headache reduction was superimposable in the PFO correction group (38.5%) and in that addressed to medical therapy (32%), p=0.32. With regard to secondary endpoints, there was a significant reduction in the number of migraine days/month after CORRECTION of PFO compared to the control group (: –3.4 ±4.4 days versus –2.0 ±5.0 days (p = 0.025). No difference was observed in the percentage of patients who achieved a 75% reduction > migraine attacks while a very significant difference was observed with regard to subjects who experienced a complete regression of migraine episodes: 8.5% (10/117) in the PFO correction group vs 1.0% (1/103) in the medical therapy group (p=0.01). Among these patient responders, 6 were symptomatic for migraine with aura while the other 4 were migraines with isolated episodes of aura.
It could be speculated that the etiological mechanism of headache in patients not subjected to PFO closure could be the activation of platelets inside the tunnel, the overlap between septum primum and secundum, of the patent foramen ovale. This segment, which may be characterized by a potential flow turbulence between the two septa, could lead to platelet activation, especially in the presence of SIA aneurysm. In a small group of patients with migraine, resistance to aspirin has been documented in 24% of subjects, suggesting platelet hyper-reactivity.
Clopidogrel and aspirin are more effective than aspirin alone in reducing headache, exacerbated after percutaneous correction of PFO in the first follow-up period[24] to demonstrate that platelet microaggregates may be responsible for post-closure migraine of PFO and may play a central role in the genesis of headache.
In women and patients with stable coronary artery disease, in antiplatelet therapy with aspirin, high platelet reactivity (HAPR) or resistance to aspirin has been described and is associated with adverse clinical outcomes. A study conducted by Jesurum et al, suggested that subjects with migraine have a higher prevalence of HAPR than healthy subjects or patients with stable coronary artery disease being treated with aspirin 325 mg. However, the clinical implications of HAPR in subjects with migraine and PFO require further investigation of analysis for the high risk of cerebral stroke and myocardial infarction and the need to prescrivere early prevention therapy.
A PFO with dx-sin shunt should require a neurological substrate susceptible and vulnerable to some substance that by-passes the pulmonary circle and induces headache. The endothelium of the

pulmonary circle has significant metabolic activity. The lung in fact metabolizes, activates or inactivates many compounds including vasoactive amines and other humoral substances[25]. Prostaglandins E1, E2 and F2 are completely removed from the bloodstream; serotonin is removed between 85% and 95%; 70% of angiotensin I is converted to angiotensin II, and 80% of bradykinin is inactivated [26]. It is not known whether these substances may increase the susceptibility of the brain to stimulate environmental or intrinsic triggers capable of triggering migraine

. Objectives and aims of the study

The aim of the study is to verify whether vasoactive/inflammatory substances together with increased platelet reactivity may play a key role in the onset of migraine and in its maintenance even after correction of PFO. The morphological and anatomical characteristics of the oval fossa will also be analyzed in order to identify elements that can correlate with increased platelet reactivity and predict a clear benefit in the control of migraine symptoms after correction of PFO. The analysis will also be extended to the evaluation of differences between female and male sex.

4. Study design

1. 4.1 Primary and secondary outcomes

Primary outcomes:

Evaluation of the % regression of migraine episodes with aura in relation to platelet reactivity in migraine patients, with and without aura, carriers of PFO, together with the dosage of PGE1, PGE2, serotonin and cytokines in order to identify potential predictive markers of beneficial effect of PFO correction on migraine symptoms.

Secondary outcomes

1. Reduction in the number of migraine days compared to pfo pre-correction, FU at 6 and 12 months.

4.2 Study design

The study is prospective observational, monocentric

4.3 Measures taken to minimise systematic errors

4.4 Treatment under study (if applicable)

4.5 Expected duration of the subject's participation

12 months

4.6 Rules for interruption (if applicable)

4.7 Procedures for checking the reliability of the experimental product (if applicable)

4.8 Preservation of randomization codes and procedures for decoding (if applicable)

4.9 Evaluation parameters

The data will be stored on electronic support. All the data reported in the data collection sheet have been obtained from the original documents and agree with the latter. The list of the individual data collected is shown in the "data collection sheet", attached to this document. (excel file)

5. Selection and withdrawal of patients

5.0 Characteristics of the population

The study population includes patients with patent foramen ovale and previous neurological event (TIA or stroke) with clinical indication to the percutaneous correction of the defect according to guidelines or ina previous TIA/stroke absence when addressed to the pfo treatment for migraine non responsive to specific therapy,as per the evaluation of the neurologist specialist. Similar evaluations are not currently available in the literature able to identify patients who, not responsive to specific drug therapy, as prescribed by the neurologist specialist, and carriers of PFO, can be directed to the percutaneous correction of the defect with indication at the moment "off-label" with respect to what is codified by the international guidelines (ESC and AHA / ACC) but potentially effective in the control of symptomatology. The advantage of PFO correction observed so far only in patients undergoing PFO correction as a result of cerebral ischemic events, could translate into migraine workers in a reduction in costs borne by the National Health System in the number of neurological medical examinations, pharmacological prescriptions and missed working days.

5.1 Inclusion criteria

Patients aged > 18 years will need to meet 2 or more criteria:

1. previous Stroke o TIA
2. Positive MRI for ischemic outcomes –
3. presence of PFO with dx-sin shunt in basal conditions > 10 MES and during Valsalva > 20 MES
4. SIA aneurysm or residual Chiari network/Eustachian valve
5. Positive Thrombophylic screening (MTHFR/prot C/Prot S)
6. ability to sign informed consent for participation in the study and adhere to the planned clinical follow-ups

5.2 Exclusion criteria

1. Patients aged > 70 years
2. Presence of paroxysmal atrial fibrillation
3. TSA vasculopathy
4. LV Systolic function < 30%
5. Moderate/severe mitral valve failure

6. Allergy or intolerance to antiplatelet therapy
7. Allergy to nickel
8. Severe renal failure (GFR < 30 ml/min)

5.3 Criteria for withdrawal

5.4 Informed consent

It is the responsibility of the researcher to obtain written informed consent from the participants before inclusion in the study, after a full explanation of the nature, objectives and risks inherent in participation in the study. The methods of processing personal data and clinical information obtained will also be explained to each participant; the participants in the study will sign the consent to the processing of personal data. It will also be emphasized that participation in the study is voluntary and it will be possible to interrupt it at any time or request at any time the elimination of any biological information or material obtained for research purposes.

6 Treatment of patients

1. 6.1 Treatment/Procedures and evaluations planned during the study

The study, which will take place at the [redacted], will be divided into two phases, described below.

Step 1: Screening of symptomatic PFO patients for migraine with aura initiated percutaneous PFO correction and clinical follow-up.
Estimated time: 24 months

This phase of the study aims to test the hypothesis that the population of subjects with PFO and indication to percutaneous correction of the defect, when symptomatic for migraine with or without aura, can be characterized as responders or non-responders with regression of the migraine symptomatology / aura.

The identification of symptomatic patients for migraine, after preliminary neurological evaluation, will be accompanied by a classification of migraine according to the severity scale of migraine sec. Anzola (Table 1). This evaluation will be repeated after PFO correction and outpatient clinical follow-up at a distance of 6 and 12 months, together with the execution of color-Doppler TT echocardiogram. This last examination will characterize the correct positioning of the PFO occlusive device and the presence/absence of residual inter-atrial shunt dx-sin.

TABLE 1. Migraine Severity Score

Intensity
0=No pain 1=Moderate (does not interfere with the performance of daily activities) 2=Severe (interferes with the performance of daily activities) 3=Inbearable (riquires enticing)
Duration

0=No pain
1=<6 hours
2=6–12 hours
3=>12 hours

Frequency

0=No pain
1=1–4/month
2=5–9/month
3=>10/month

Aura

0=No aura

OCCLUDER DEVICE FOR PFO

1. The Occlutech Figulla device consists of a single layer of nitinol meshes that conform to give rise to 2 flexible discs (the left disc withdia metro smaller than 2 mm) with a perno only on the right side. The discs are connected to each other thanks to a flexible and compressible central portion the size of 3 mm. The left disc is a flat monolayer covered with an ultra-thin piece of polyethylene terephthalate. The size of the Figulla device is determined by the diameter of the two discs in the following configurations: 16/18, 23/25, 27/30 and 31/35 mm.

PFO CORRECTION PROCEDURE

1. Pfo correction will be performed percutaneously under local anesthesia with bilateral femoral venous puncture by placement of introducer 6F in the right femoral vein and 8F in the left femoral vein. The 8F introducer will be replaced at sin with the placement of 45-cm,8.5 F Slow-curve introducer for the advancement of the intracardiac ultrasonographic catheter (Ultra ICE^{TM,}Boston Scientific, Marlborough, MA, USA). This probe, with the advantage of avoiding the intubation of the patient, will allow to characterize the anatomy of the SIA and allow the measurements of the oval fossa and the presence / absence of aneurysm of the SIA for the most appropriate choice of the occlusive device suitable for size and to monitor the positioning and implantation of the occlusive device. A 0.035" guide wire with J tip will be positioned through the inteartrial septa into the superior pulmonary vein. In all cases an occlusive device of adequate size will be loaded inside a moon cannula of the size between 7-10 F and advanced pushing the release cable to the end of the introducer positioned in the left atrium. Under fluoroscopic and intracardiac ultrasound guidance, the left disc of the device will be implanted and approached against the left side of the SIA. With a slight voltage maneuver on the release cable, the cannula will be retracted allowing the right disc to be implanted. The intracardiac ultrasound evaluation will allow to evaluate the correct positioning of the device and the absence of images related to coronary obstruction and / or pulmonary venous return or compression of the aortic root and atrioventricular valves. At this point the device will be permanently released.

INTRA E POST-PROCEDURE THERAPY

Patients will receive 70 IU/Kg of heparin at the beginning of the procedure in order to maintain the ACT (activated platelet aggregation time) value > 200 seconds. Aspirin 100 mg will already be therapy in place for more than 7 days and continued for at least 6 months after the correction of PFO while Clopidogrel 75 mg will be administered immediately after the procedure and continued for 2-3 months in patients treated with implantation of devices > 25 mm diameter. Antibiotic prophylaxis will be started before the procedure and continued for the next 5 days.

FOLLOW-UP

The clinical and diagnostic follow-up with cardiological examination, color-Doppler echocardiogram at 6 and 12 months and compilation of the Migraine severity score scale (Table 1), will allow to evaluate any residual shunts post correction of PFO and the beneficial effects on the control of migraine symptoms by reassessment of the Anzola score.

Phase 2: Analysis of platelet reactivity and levels of inflammatory cytokines,PGE1, PGE2 and serotonin in migraine patients with PFO.

Estimated time: 24 months

This phase of the study aims to investigate whether the beneficial effect of PFO correction on migraine is secondary to a barrier mechanism to platelet microembolization and that this response may correlate with the parameters of platelet function and activation. For this purpose, the study of platelet function will be carried out before the correction of PFO and 180 days after surgery.

For the evaluation of the parameters of platelet function from each patient, a blood sample will be taken in the absence of stasis, in order to avoid platelet activation, from the antecubital vein of the forearm by means of a G19 needle. Before proceeding with the separation of the platelets, a quantitative hematology analysis will be performed with leukocyte formula and platelet count by means of Sysmex XS 1000 automatic blood count.

Cytofluorimetry studies will allow to characterize the state of platelet activation in terms of protein expression both on the cell surface and inside the cell. In particular, the expression of P-selectin, activated GpIIbIIIa, Tissue Factor and Phosphatidylserine will be evaluated through the use of specific monoclonal antibodies. These analyses will be performed both in basal conditions and after *in vitro* activation with agonists such as ADP, thrombin and epinephrine. The same conditions will also be used for the evaluation of the presence of mixed aggregates, platelet-leukocytes, sensitive index of platelet activation.

PRP (Platelet-Rich Plasma), separated from the blood by centrifugation, will be used to perform platelet aggregation studies in response to different agonists such as ADP, collagen, thrombin, epinephrine and arachidonic acid.

The characterization of the circulating microvesicles will be performed on samples of Platelet-Free Plasma (PLP), by means of a multiparametric analysis performed using the new generation cytofluorimeters. In particular, not only the total number of microvesicles present in the sample will be considered, but a detailed phenotyping will be performed that will give information on the

cellular derivation of the microvesicles, considering in particular those of platelet, leukocyte and endothelial origin.

Serum TXB_2 levels and urinary excretion of 11-dehydro-TXB_2 will be evaluated by mass spectrometry.

The levels of the inflammatory cytokines IL-1, IL-6, TNFa will be measured on plasma samples with enzyme immunoassay, while the levels of PGE_1,PGE_2 and serotonin will be dosed by HPLC method.

6.2 Treatments allowed and not before/during the trial

6.3Procedures to monitor patient compliance (if applicable)

7. Efficacy/endpoint evaluation

7.1 Specifying Effectiveness/Endpoint Parameters

Primary endpoints:

Secondary endpoints

7.2 Methods and times for the assessment, recording and analysis of effectiveness parameters

8. Safety/tolerability assessment

8.1 Specification of safety parameters

8.2 Methods and times for the assessment, recording and analysis of safety parameters

8.3 Procedures for reporting for the registration and reporting of adverse events and intercurrent diseases

8.4 Type and duration of subjects following adverse events

9. statistical analysis

9.1 statistical analysis

Continuous variables will be summarized using the DS ± mean. Categorical variables are represented using frequencies and percentages. For the comparison between responders andnon-responders,the Student's 2-code t-test or the Wilcoxon test for continuous variables will be used. The Chi-square test or the Fisher test will beused forcategorical variables.

9.2 Calculation of the sample number

The sample size calculation is based on the 1-year primary endpoint. A value for the frequency of reachingtheprimary endpoint was placed around 60%, in accordance withthe data reportedin

literature[22, 27]. A sample of 92 patients was identified, necessary to obtain a potencyof 80% able to detect as significant ($p<0.01$, considering the Bonferroni correction for multiple tests) a correlation coefficient of 0.35 (adjusted for 4 confounding variables) between the variation of the migraine score sec. Anzola and any of the 5 factors (platelet reactivity, PGE1, PGE2, cytokines, serotonin) measured at baseline.

9.3 Significance level to use

Statistical significance will be considered that obtained with a p value of 0.05.

9.4 Criteria for the conclusion of the trial

9.5 Steps to handle missing, unused, or spurious data

10. Direct access to original data and documents

The investigator will allow monitoring, verification, review by the Ethics Committee or any other control body, allowing direct access to the original data and documents.

11. Quality Control and Assurance Procedures

Regular internal monitoring visits will be carried out.

12. Ethical Aspects

The Study will be conducted in full respect of human dignity and its fundamental rights as dictated by the "Treaty of Helsinki" and subsequent amendments, by the "Good Clinical Practice" (GCP) rules issued by the European Community and in accordance with all local laws and regulations concerning clinical trials.

13. Data retention and analysis

Sensitive data, managed on computer support, will be processed as per current legislation and therefore the personal information will be separated from those that determine a clinical picture of the patient. The original data will be kept for 7 years by the investigators and, on request, made public. The reference that links the clinical data to a patient will be kept in a Microsoft Excel format file on the personal computer of the project coordinator. The patient's personal data are not of interest for the trial in question.

14. Privacy

The researcher undertakes to obtain and record on paper or computer and in a clear manner the information required in this protocol and to ensure safe storage and confidential access to information. The patient's surname(s), first name(s) and date of birth will only be present in the source document (medical record). Each biological information or material will be identified with a unique code that will allow to associate the clinical data with the laboratory results but, in no case, with the identity of the patient.

15. Insurance

For the risks deriving from participation in the study, the Monzino Cardiology Center, IRCCS has an adequate insurance coverage stipulated in accordance with the laws in force on the subject. By contract, the insurance will respond only in cases where the damage suffered by the patient is related to any procedure associated with his participation in the study. The insurance will not

reimburse damages resulting from procedures conducted by the patient not covered by this Protocol.

16.Publication criteria

The results of the study will be used by the investigators only within the objectives indicated in the protocol.

17. Intellectual property

All publications and /or communications related to the study will be previously approved by the P.I. of the Institution involved and in particular by the PI Dr. Daniela Trabattoni of the Monzino Cardiology Center.
The product of data processing in connection with this Study, including documentation, information, materials and results in any form generated in the course of the study, will be the property of the investigators.

18.Administrative requirements

Beginning of the study
The study will begin only after the written approval of the Ethics Committee.

Standards of Good Clinical Practice and European Directives for Clinical Trials
The investigators assure that the study will be conducted in accordance with the Helsinki Declaration (1964), Amendment of Sommerset West, South Africa (1996) and with the international standards of standards of Good Clinical Practice, of the ICH (International Conference on Harmonization) and in accordance with all local laws and regulations concerning clinical trials. The study will not begin until there is approval, by the Ethics Committee, of the protocol, the information sheet for the subjects, the consent procedure and the written informed consent form.

Amendments to the Protocol
Any proposed amendment will only be implemented if approved by the Ethics Committee

confidentiality
The investigators involved are committed to preserving the confidentiality of the patients taking part in the study.

responsibility
The person responsible for the processing of the personal data of the participants in this study is [redacted]

The scientific manager of this study [redacted]

The statistical manager of this study is [redacted]

Conflict of interest
Researchers involved in this project declare the absence of conflicts of interest.

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