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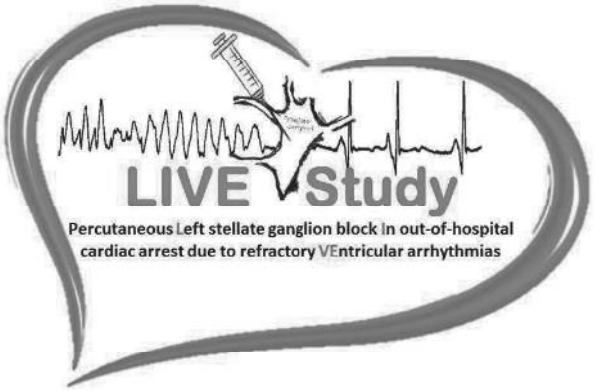

Pavia, 11/5/2018

Percutaneous Left stellate ganglion block In out-of-hospital cardiac arrest due to refractory VEntricular arrhythmias (LIVE Study)

Protocollo: Blocco percutaneo del ganglio stellato di sinistra nell'arresto cardiaco extra-ospedaliero causato da aritmia ventricolare refrattaria (LIVE Study)

Prospective uncontrolled study

Purpose: evaluation of the use of percutaneous left stellate ganglion block during out-of-hospital cardiac arrest with shockable rhythm refractory to standard treatment with the goal of assessing safety, feasibility and preliminary efficacy

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1. Background

The influence of the autonomic nervous system (ANS) on heart rhythm is known since decades and the effectiveness of its modulation with beta-blockers to reduce arrhythmias and mortality is widely demonstrated [1-3]. In the last twenty years, it has also been shown that it is possible to modulate the ANS also with non-pharmacological interventions: left cardiac sympathetic denervation (LCSD), i.e. the surgical resection of the lower half of the stellate (cervicothoracic) ganglion and T2 to T4 sympathetic ganglia, has been shown to be effective in reducing ventricular arrhythmias, both in inherited arrhythmogenic cardiopathies and in structural heart disease (both ischemic and non-ischemic) [3-8]. Many elements play a role in LSCD effectiveness in arrhythmias reduction: the most important being an increase in ventricular fibrillation (VF) threshold, a reduction in transmural repolarization heterogeneity and an increase in the effective refractory period [9-11]. Since 2000 onwards, there is also increasing evidence about the percutaneous stellate ganglion block (PSGB) as an effective weapon for the treatment of ventricular arrhythmias refractory to traditional interventions in an emergency setting; the most recent evidence supports the use of PSGB on top of contemporary therapies in the management of refractory ventricular arrhythmias [12-18]. This technique, which consists in the injection of 5-10 mL of local anaesthetic at the C6 level, is known since the first half of the twentieth century and is widely used for the treatment of sympathetic-related pain syndromes. At the level of C6 the site of puncture is far away from the lung with a resulting lower rate of pneumothorax compared with insertion at level of C7. The needle is advanced onto Chassaignac's tubercle, and it is then withdrawn to inject the local anaesthetic. The operator can use ultrasounds as a guide for needle insertion or use a technique based on anatomic landmarks and no superiority of one technique over the other has been demonstrated [19-24]. Assessment of the block's efficacy can be performed by observing the occurrence of miosis ipsilateral to the side of the block, as not only the sympathetic efferent fibers to the heart, but also sympathetic efferent fibers to the eye are blocked [17]. Regarding the use of PSGB during a refractory cardiac arrest with shockable rhythm there is a promising evidence by Amino et al. [12]: in all patients in whom miosis was observed after PSGB, the subsequent shock was effective in terminating the ventricular arrhythmia, at variance with the cases in which miosis was not observed and the shock continued to be ineffective in terminating the arrhythmia. In this population PSGB was performed after the admission of the patient into the hospital with ongoing CPR, whilst, to date, no studies are present about the use of PSGB during refractory cardiac arrest with shockable rhythm in the pre-hospital setting. This lack of data is likely favoured by the fact that in the majority of Emergency Medical System (EMS) at global level it is very uncommon to have anaesthesiologist or intensive care doctors, working in the pre-hospital setting.

The analysis of data collected in our Cardiac Arrest Registry of the Province of Pavia (Pavia CARe - NCT03197142) from 1 January 2015 to 31 December 2016 revealed that patients who suffered of an out-of-hospital cardiac arrest (OHCA) with a first shockable rhythm and who needed 5 shocks or more to terminate the arrhythmia (n=66) showed a significantly lower rate of sustained return to

spontaneous circulation (ROSC) until admission and transfer of care to the receiving hospital (defined as "survived event" following Utstein-style) as compared to those who needed 4 or less than 4 shocks (n=101) to restore a perfusing rhythm until admission (40.9% vs 59.4%, p=0.03). The differences in survival to hospital discharge and survival at one month with good neurological outcome were even greater (21.2% vs 45.5%, p=0.002 and 18.2% vs 39.6%, p=0.006, respectively).

Considering our data and the evidence present in the literature, the use of PSGB in adjunct to traditional treatment appears a promising approach for patients with refractory OHCA due to a shockable rhythm.

2. Methods

2.1 Training of medical doctors

Prior to the beginning of enrolment, all the medical doctors (MD) involved in the EMS of the Province of Pavia will be trained in the PSGB procedure. In order to standardize the procedure, all the MD will participate in a training course. The aim of the course will be to acquire the technique to identify the correct point for needle insertion on the neck of a volunteer with and without the support of ultrasound. All the possible complications and their management will be discussed. The training will be provided by physicians with proven competences in PSGB and a 3D model of the neck printed ad-hoc will also be used to optimize the learning of the technique. The course will be endorsed by the School of Anesthesia and Intensive Care of the University of Pavia.

2.2 Inclusion criteria

- All patients with an OHCA occurred in the Province of Pavia in which the first rhythm was a shockable one

2.3 Exclusion criteria

- Patients in which the cause of the cardiac arrest is non-medical following Utstein-style 2014 (trauma, overdose, drowning, electrocution, asphyxia)
- Patients who has an anisocoria at the arrival of medical doctor on the scene
- Patients whose neck is judge unsuitable for PSGB by the operator (i.e. presence of big scar, thyroid goiter, etc.)

2.4 Study flow

This is a prospective uncontrolled study. All patients meeting the inclusion criteria will be consecutively enrolled in the study. The EMS rescue team medical doctor (MD) will be asked to perform PSGB after all the actions provided in the ACLS algorithm and which are considered useful in the clinical situation (intubation and ventilation, administration of iv/io adrenaline, amiodarone or lidocaine, use of mechanical chest compression, etc.). The PGSB will be performed after the administration of the 4th shock if the 3rd shock was unsuccessful in restoring a stable perfusing rhythm, considering all the shocks administered both by an AED or by manual defibrillator. The

evaluation of the effectiveness of the 3rd shock will be carried out at the end of the two-minute cycle after shock delivery, as recommended by the guidelines. If the MD will arrive on the scene after the delivery of the 3rd shock, the PSGB should be executed as soon as possible after performing all the actions which are considered useful in the clinical situation. The MD, based on his confidence, can choose to use the anatomic technique or the echo-guided technique. The technique will be performed in the pre-hospital setting. Those patients with refractory OHCA transported with ongoing ACLS who receive the fourth shock once in the emergency department will be also considered. On the contrary patients with prehospital ROSC who suffer a new cardiac arrest once in the emergency department won't be considered in the present study. The MD will be asked to evaluate the presence of aniscoria immediately before the PSGB and 1-2 minutes after the PSGB. In case of absence of anisocoria 2 minutes after PSGB, MD can try PSGB another time. The anaesthetic that will be used for PSGB is lidocaine 2%, which is already available among EMS drugs. After the end of the event, the MD will be asked to fill in a questionnaire regarding the feasibility of the technique in the pre-hospital setting, the practicability of its implementation compared to the usual procedures performed in the pre-hospital setting and any problems encountered. The responses will be scored from 1 to 10 (1=perfect feasibility; 10=no feasibility). All eventual complications associated with PSGB will be carefully recorded.

The effectiveness of the PSGB will be evaluated if at least one shock will be delivered after the execution of PSGB.

The data will be compared to our historical cohort of patients with the same OHCA characteristics (first shockable rhythm and who received more than 4 shocks) enrolled in the Cardiac Arrest Registry of the Province of Pavia from 1 January 2016 to 31 December 2017.

2.5 Involved units

- AAT di Pavia 118 Unit – Fondazione IRCCS Policlinico San Matteo – Pavia
- Cardiac Intensive Care Unit (UTIC) – Fondazione IRCCS Policlinico San Matteo – Pavia
- Intensive Care Unit – Fondazione IRCCS Policlinico San Matteo – Pavia
- Azienda Regionale Emergenza Urgenza (AREU) – Milano

2.6 Possible complications

The procedure is burdened by very few complications and the major two are the following:

- Possible intravascular injection of the local anaesthetic: the operator will insert the needle in the neck while aspirating with the syringe and he will inject only when sure of being extravascular, so the rate of this complication should be reduced almost to zero. Moreover, it is to be noted that some paper of the past decades suggested that intravenous lidocaine could provide a cerebral protection effect in cardiac arrest patients. So, in this specific setting, this complication is presumed to have minimal effects.

- Vascular perforation: it is possible that the needle passes through a vascular structure of the neck causing a local bleeding. However, the small dimension of the needle and the low blood flow during resuscitation should limit the bleeding. Moreover, it will be very likely for the patient to have an advance airway in place before the procedure so, in case of bleeding, airways obstruction will be prevented.

Other minor complications could be:

- Pneumothorax: this rare complication is by far more frequent in case of needle insertion at T1 level. The procedure described in this protocol will be done at C6 level so the risk of pneumothorax is unremarkable.
- Allergy to the drug: considering that the anaesthetic injection will be extravascular and the patient is in cardiac arrest, an eventual allergy may presumably occur only at the local level without major risks for the patient.

3. Outcome

3.1 Primary Safety and Feasibility Outcomes

- The occurrence of complications associated with PSGB in the pre-hospital setting
- The feasibility and practicability of PSGB in the pre-hospital setting

3.2 Primary Efficacy Outcome

- To assess whether the rate of ROSC until admission and transfer of care to the receiving hospital is higher in the patients treated with PSGB as compared to historical controls.

3.3 Secondary Efficacy Outcomes

- To assess whether the rate of ROSC until admission and transfer of care to the receiving hospital is higher in the patients treated with PSGB and in which anisocoria is present after the PSGB, but not before PSGB
- To assess whether the survival rate at hospital discharge is higher in the patients treated with PSGB.
- To assess whether the survival rate with good neurological outcome (CPC 1 ore 2) at 1 month after the event is higher in the patients treated with PSGB.
- To assess whether the survival rate at hospital discharge is higher in the patients treated with PSGB and in which anisocoria is present after the PSGB, but not before PSGB
- To assess whether the survival rate with good neurological outcome (CPC 1 ore 2) at 1 month after the event is higher in the patients treated with PSGB and in which anisocoria is present after the PSGB, but not before PSGB.

4. Sample Size

The sample size calculation is based on the primary efficacy endpoint. In order to have 80% power to observe an increase in the rate of ROSC from 40.9% (historical controls) to 70.9%, i.e. an absolute increase of 30%, with an alpha level of 0.05, 40 new patients will be needed. Accounting for a 25% loss, we will need 53 cases of OHCA with more than four shocks delivered. This will require approximately 20 months.

5. Statistical analysis

The main descriptive statistics as mean and standard deviation or median and interquartile range will be used to describe all the variables collected during the study. The chi-square test will be used to evaluate differences between categorical variables, while the Student's T-test to evaluate differences between continuous variables. If the condition of normality will be not respected, an analogous non-parametric test (Mann-Whitney or Kruskall-Wallis test) will be used. The p-value of 0.05 will be considered significant. All the statistical analyses will be performed using a statistical software (MedCal software version 12.5.0.0 by MedCal software bvba or SPSS 22.0 Windows version, SPSS Inc., Armonk, NY).

6. CRF e data management

Data will be collected in paper and digital form. All procedures concerning data management and security will adhere to the EU Data Protection Directive 95/46/EC.

None of the recorded and collected data can be linked to the individual they belong to. Each patient will be assigned a unique identification number that will be used to identify the data. The patient's identity is stored in a separate database under the responsibility of the principal investigator along with an identification number and a copy of the data to answer the questions during the "cleaning database" process.

All standard procedures regarding collection, registration, and data security will be observed. In particular, appropriate measures will be taken to protect the data from their accidental or unlawful destruction, accidental loss or alteration, unauthorized access, abuse, and any other misuse.

Data processing cannot take place in "ad hoc" locations (home workstations).

If processing a sensitive data, as a rare exception, should take place in "ad hoc" workstations (home workstations), the computer must comply with the control requirements regarding the protection of personal data, ensuring that personal data protection is sufficient.

7. Informed consent

For the intervention

Considering that the intervention proposed in this protocol is implemented in an emergency setting, where it is impossible to communicate with the patient or a legal representative, the decision to perform the intervention will be taken by the medical doctor, strictly adhering to the provisions of this protocol.

The medical doctor, before performing the intervention, will ascertain, as far as possible considering the emergency situation, that the patient has not expressed the willingness not to take part as subject to any experimentations or that he/she has not given advance treatment directives concerning the agreement or disagreement to the therapeutic/experimental treatment.

For the use of personal data

The consent to the anonymous use of personal data will be required to the survived patient or, if appointed, to the legal guardian. Patients will then receive the information form and informed consent form to the processing of sensitive data.

The investigator will observe the applicable regulations for the research and documentation of informed consent, adhere to the rules of Good Clinical Practice and the ethical principles derived from the Helsinki Declaration. If an informed consensus module update is required during the study, approval by the Ethics Committee will be required before submitting patient updates.

In accordance with the recommendations of the Helsinki Declaration and local regulations, each patient will be adequately informed of the aims, methods, expected benefits, potential risks and disadvantages associated with the study; the patient will be informed of his right to refuse consent to the use of his or her sensitive data, or to withdraw it at any time, without affecting his or her medical care.

The patient will have all the time needed to evaluate the information received before providing his/her informed consent to the use of sensitive data.

The investigator must receive informed written consent from the survived patients before using them in any way for the purpose of the study. The written consent to the processing of sensitive data must be documented by the date and signature of the patient's and by the date and signature of the investigator or whoever is the author.

The investigator will provide the patient with a signed copy of informed consent and will retain the original together with the other protocol documents; such consent will be obtained after telephone interview or by personal meeting or, if not possible, by postal mail. All possible and reasonable attempts will be made to trace patients.

For deceased patients, data processing will be processed by anonymizing the data through decoding files that will be destroyed at the end of the data collection.

8. Costs

As compared to standard care the only extra fees concern the needles (12 euro/needle) and the training. Both of them will be charged on the proposing unit. Regarding lidocaine, it is already available among EMS drugs, so it will be provided by "AAT di Pavia 118" Unit and AREU without extra-costs.

9. Involved Personnel

Scientific study director: Dott. Simone Savastano
Data manager and investigator: Dott. Enrico Baldi

Investigators:

I. Dott. Caneva Luca
II. Dott. Civardi Luca
III. Dott. Comelli Andrea
IV. Dott. Contri Enrico
V. Dott. Cortesi Sergio
VI. Dott. Fumagalli Paolo
VII. Dott. Lusona Bruno
VIII. Dott. Maggio Giuseppe
IX. Dott. Pozzi Marco
X. Dott. Repossi Filippo
XI. Dott. Rizzardi Roberto
XII. Dott. Sciutti Fabio
XIII. Dott. Tavazzi Guido
XIV. Dott. Vito Sgromo
XV. Dott.ssa Aliberti Anna
XVI. Dott.ssa Brancaglione Antonella
XVII. Dott.ssa Brancati Stefania
XVIII. Dott.ssa Dusi Veronica
XIX. Dott.ssa Fuardo Marinella
XX. Dott.ssa Guerci Manuela
XXI. Dott.ssa Mongodi Silvia
XXII. Dott.ssa Orlando Anita
XXIII. Dott.ssa Palo Alessandra
XXIV. Dott.ssa Pamploni Greta
XXV. Dott.ssa Pettenazza Pietro
XXVI. Dott.ssa Richiusa Sara
XXVII. Dott.ssa Romeo Immacolata
XXVIII. Dott.ssa Sportiello Debora
XXIX. Dott.ssa Toscani Monica

10. Insurance

Considering that all the medical doctors involved in the present study are currently working for the Fondazione IRCCS Policlinico San Matteo and basing on the existing convention between the Foundation IRCCS Policlinico San Matteo and Azienda Regionale Emergenza Urgenza (AREU) (prot. 211/2009) all the legal and administrative issues concerning the medical responsibility are charged to the Fondazione IRCCS Policlinico San Matteo (the employer) even if the study procedure will be performed outside the hospital.

11.Publications

Data and publications will be managed by the proposing group.

The protocol of the study will be made available on clinicaltrials.gov or another similar platform for appropriate knowledge and discussion.

The results of the study will be published, independently of the positive or negative result of the same, in order to avoid unnecessary duplication.

12.Conclusion

Our study will be the first to evaluate the use of percutaneous left stellate ganglion block during out-of-hospital cardiac arrest with shockable rhythm refractory to standard treatment with the goal of assessing safety, feasibility and preliminary efficacy.

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