

EUPHAS 2: clinical application of endotoxin removal in septic shock
- Web-based collaborative data collection project -

Scientific Committee:

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EUPHAS 2 PROJECT (TM07)

Device name: Toraymyxin (PMX-20-R) –device for endotoxin adsorption by hemoperfusion

Project of the study: Multicentered, open, collaborative data collection.

Ethics: The protocol for collecting data will be submitted to the ethics committee. The review of the Ethics Committee, as a part of a collaborative data collection, primarily ensures the protection of patient privacy and thoroughly checks the protocol in order to verify the absence of any interventional purpose within the study. Consequently, the implementation of this data collection could not alter in any way the kind of care and treatments which the patient undergoes.

ABSTRACT

EUPHAS 2 project will be a collaborative web database in which every registered user will be allowed to introduce and analyze data of patients treated in their center. The Web portal will automatically update the enrollment statistics, while the entire data set will be available for the steering committee only (SSC) and presented to all registered users once a year in a PMX-20-R user group meeting. This meeting will decide how to use and disseminate all collected PMX-20-R data.

The SSC will be in charge of defining the data collection, analysis and management of results, as well as determining a project dissemination program. The SSC will be composed of 4 investigators: 2 researchers of the original EUPHAS trial and 2 other experienced PMX-20-R users (outside of the EUPHAS trial).

The EUPHAS 2 study will be characterized by two phases. Phase 1 will be a retrospective collection of data from severe sepsis or septic shock patients treated with polymyxin B hemoperfusion in Italian ICUs within the last 3 years. The aim of this phase is to obtain historical data for at least 250 patients. This preliminary data collection is estimated to require 6 months to complete, after which the SSC will analyze the collected data in order to define the criteria conditions which will be utilized in the subsequent data collection (phase 2).

Phase 2 will be a multicentered, open, web database and data collection of all patients treated with polymyxin B direct extracorporeal hemoperfusion (PMX-DHP) in participating Italian and European ICUs. All patients will be completely managed according to standard protocols of each ICU, including fluid infusion, vasopressor administration, mechanical ventilation, antimicrobial chemotherapy and support of renal function, such as artificial CRRT and/or hemodialysis. Therefore, the inclusion of patients in the database will not, under any circumstances, impose any change on patient management, and each patient will receive a follow-up for 29 days (from day 0 to day 28) following entry into the study.

The aim of EUPHAS 2 project is to collect a great quantity of data regarding PMX-20-R treatments by recording when, where and how PMX-20-R is used, and to subsequently correlate these data with procedure effectiveness. EUPHAS 2 will be reviewed at agreed stage periods, namely once a year, during which all data will be classified, interpreted and commented upon by the steering committee and presented to all project participants by means of the organization of a user group meeting (UGM). It will then be submitted to influential reviews for publication.

The EUPHAS 2 project web site and database will be set-up in both Italian and English allowing the collection of data not only from Italian sites but also from users from various countries. According, each site will be entered into the project upon acceptance by the steering committee.

1. BACKGROUND

The PMX-20-R cartridge is a device for extracorporeal hemoperfusion, in which the PMX-B (Polymyxin B) is fixed on modified polystyrene fibers. The cartridge is composed of a polycarbonate shell that contains an absorbent consisting in a tissue composed by the fibers described above and wrapped around a central pipe. PMX-B is chemically immobilized to the polystyrene fibers by covalent binding. Based on the knowledge that PMX-B binds to endotoxin with great affinity, several studies have shown that hemoperfusion with the immobilized PMX-B efficiently removes circulating endotoxin from the blood [1-3].

The clinical efficacy of this therapy was first described in several small clinical trials mainly conducted in Japan, however, the methodologies of these studies have been considered sub-optimal. In 2007 Cruz and colleagues [1] published a meta-analysis that, for the first time, summarize the experiences currently available regarding this therapy. Despite the obvious limitations of systemic reviews, this analysis revealed that endotoxin removal therapy appears to contribute to the hemodynamic stabilization of septic patients and improved overall survival.

In the last 2 years, two randomized trials performed in Italy (Cantaluppi et al. 2007 [2], Cruz, Antonelli et Al. 2009 [3]) have been published, which further confirmed the results of the meta-analysis. In particular, the study by Cantaluppi reports the effects of endotoxin removal therapy on the recovery of renal function, demonstrating the mechanism of action involves the inhibition of apoptosis and preservation of proper cell proliferation. The EUPHAS study (Cruz, Antonelli et al), published in June, 2009 in JAMA, was designed to study the effects of PMX-DHP therapy on a selected group of patients with septic shock secondary to emergency abdominal surgery, and demonstrated a strong protective effect. Since 1994, PMX-20-R is available on the market and is approved by the Japanese health insurance system. The PMX-20-R device obtained the CE mark since 1988 as a class IIB medical device. After its first commercialization in Japan, about 75 000 cartridges have been used. Currently, approximately 600 cartridges per year are used in Italy. Considering both clinical trials and surveillance systems of medical devices, noteworthy side effect or adverse events have never been reported. Nevertheless, the international scientific community remains skeptic about the effectiveness of extracorporeal endotoxin removal therapy in clinical practice.

2. AIM OF THE STUDY

2.1. Aim of the study

Objective: Evaluate the efficacy of endotoxin removal by the Polymyxin-B adsorbing device in clinical practice, in order to both verify the reproducibility of data available in literature, evaluate the population actually elected for the therapy and identify subpopulations of patients who may benefit of treatment more than others.

EUPHAS 2 project consists of a multi-centered, open and collaborative data collection having the purpose of anonymously tracking the characteristics of pathologies among patients treated by Toraymyxin® as well as the outcomes of the treatment in terms of survival, length of stay and duration of concomitant therapies. (amine administration, mechanical ventilation, CRRT)

All patients will be managed by applying the usual protocols of intensive care, without exceptions, including the infusion of fluids, administration of vasopressors, mechanical ventilation, antimicrobial therapy, support of renal function such as artificial CRRT and hemodialysis. The inclusion of patients in the database shall not, under any circumstances, impose any change on patient management.

The EUPHAS 2 study will be characterized by two phases. Phase 1 will be a retrospective collection of data from severe sepsis or septic shock patients treated with polymyxin B hemoperfusion in Italian ICUs within the last 3 years. The aim of this phase is to obtain historical data for at least 250 patients. This preliminary data collection is estimated to require 6 months to complete, after which the SSC will analyze the collected data in order to better define the Case Report Field which will be utilized in the subsequent project phase.

Phase 2 will be an open, multicentered, web database and data collection of all patients treated with PMX-DHP in participating ICUs. All patients will be completely managed according to standard protocols of each ICU, which includes fluid infusion, vasopressor administration, mechanical ventilation, antimicrobial therapy and support of renal function, such as artificial CRRT and/or hemodialysis. Therefore, the inclusion of patients in the database will not, under any circumstances, impose any change on patient management. The data base will track each patient for 29 days (from day 0 to day 28) following the PMX treatment.

2.2. Characteristics of data collection

A web database will be implemented and will be accessible to registered users only. All users are able to enter, edit and analyze data of their patients alone. The Web portal will automatically generate and update the statistics for some basic inclusion data (i.e. number of patients traced, average enrollments for hospital) The entire database will be examined and analyzed by statistical professionals, under the supervision of the Scientific Steering Committee (SSC) at fixed time intervals of approximately one year. The collected data fields will be divided into three categories: mandatory, optional and customized. Customized fields are extra database fields that each center could add in order to personalize their data collection.

2.3. Surveillance system

Data entry errors will be minimized implementing appropriate procedures of data check (drop-down menus, range checks on measurement units, etc.). An e-mail reminder, automatically issued by the system or managed by SSC secretariat will be to the users e-mail in order to remember the data entry of follow-up for each patient. A Clinical Monitor, under the control and supervision of the Steering Committee, will be responsible for verifying the entered data, their completeness and their consistency.

2.4 Property and usage of data stored in the Database

Estor SpA, sponsor of the project, will not claim any ownership on collected data or use them without the approval of the owners of individual data. The same applies to members of the Steering Committee. At the same time, Estor SpA will be able to consult the Database at any time for internal information. Members of the SSC will have access to the database in order to evaluate and analyze its content. The Steering Committee will yearly present the collected data to users during special users group meetings. Individual centers will be the owners and managers of data they enter: they can see, analyze or modify them any time needed until the final submission/approval of the Clinical Monitor.

3. STRUCTURE OF DATA COLLECTION

This project is an open, multicentered and collaborative data collection, which will study the usage of PMX-20-R treatment in clinical practice. This will include patients with severe sepsis or septic shock originating in the abdominal cavity, urinary tract or otherwise supported by high activity levels of endotoxin (EAA>0.6) measured by chemiluminescence in whole blood (according to the method described by Marshall et al [4]), and accompanied by the dysfunction of one or more organs. All patients will be managed applying the standard protocols of intensive care, including the infusion of fluids, administration of vasopressors, mechanical ventilation, antimicrobial chemotherapy, the support of renal function such as artificial CRRT and hemodialysis, if necessary.

Each patient will receive a follow-up for 29 days (from day 0 to day 28) after the entry into the study.

From a practical point of view, the data collection will be done via web, through the creation of a new portal used both as a data collection and a statistical consultation access point. The portal will consist of a Homepage with public access containing the project description and some basic statistical information (project start date, number of related centers, number of patients enrolled). A News section will also contain information about meetings, conferences or congresses. A login box, allowing users' authentication, will be located on this Homepage.

Once authenticated, in addition to the above described information, a special menu with the following features will appear

- Insert new patient
- Show Details
- Export

Regarding the data, each user will be able to see links to: old data, enter new data, modify and delete data. The data will be presented in a list page with filters to search and link to the corresponding detail page. It will be also possible for users to download their data in Excel format.

A mechanism of data approval will be created, in that once the user completes data entry, the SSC approval can be requested, which will check, approve or reject data. Once approved, data can be amended only with the consent the SSC.

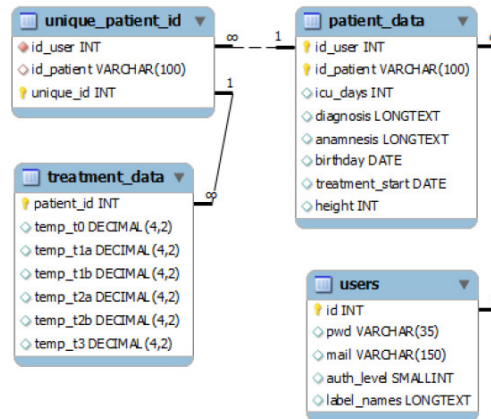
The portal will be deployed in two languages and each user will be associated with a default language for content presentation; language can be always changed by clicking on an appropriate link.

The portal will be equipped with an area of content management (hereinafter CMS, Content Management System), that is, special pages with restricted access available to create and manage other administrative users of the site (with three possible access levels: superuser, master-superuser and administrator). This includes:

- Change the text of the home page
- Manage users (insert, edit, delete)
- View the log user access to the site
- Export data in Excel format

The portal will be designed to be afterwards upgraded and updated and will be compiled with code compatible with different PC and Macintosh hardware platforms and major browsers: IE, Firefox, Opera, Safari, paying particular attention to the speed of page loading. The development language chosen is PHP associated with a MySQL database, either open source with freeware licensing.

The database structure will be set as shown in the figure below, in order to easily collect the data reported in the CRF shown in Appendix.



Carrying out the database, programmers should pay particular attention to two crucial aspects:

- Minimize the risk of errors in data entering (i.e check the appropriateness of the units or provide cross-checks between some fields)
- Minimize the time required for data entry of each patient, preferably not exceeding 20 minutes per patient.

The database will be set to collect data describing the overall condition of each patient (medical history, diagnosis, demographics, etc.), data during treatment and follow-up data. Some fields are mandatory, while others are optional or customized.

3.1. Inclusion data

Preliminary information needed to enter a patient in the database will include the following information:

- demographics: age, sex, body size (height, weight)
- inclusion criteria, including the date of diagnosis of septic shock and endotoxin activity value (if available)
- results of biological cultures
- underlying diseases, including type of infection and causes of intra-abdominal surgery
- main treatments and concomitant treatments with other medical devices.
- patient severity scores

3.2. Data collected before (PRE) and after (POST) PMX-20R treatments

The measurement of pre and post-treatment variables will be performed according to standard laboratory procedures, i.e. blood analysis; the following parameters will be also recorded: vital signs, vaso-active drugs, diuresis, SOFA score, hemodynamic variables and values of gas analysis. Measurements at day 0 will be considered baseline. See details in the table 1 below.

3.3. Follow-up data

Data collected as treatment follow-up will aim to assess the effectiveness of endotoxin removal treatment in clinical practice. For this purpose, some data will concern the evolution of clinical framework of patients within 4 days following the treatments, charting outcome variables needed to assess not only clinical efficacy but also the economic impact.

Table 1

Vital signs:	body temperature, heart rate, respiratory rate (or ventilator data), BP (SBP, MAP) will be recorded at day 0 and daily from day 1 to day 3.
Vaso-active drugs:	Doses of noradrenaline, dopamine and other vasoactive drugs will be recorded at day 0 and daily from day 1 to day 3.
Diuresis:	The daily urinary volume and plasma concentration of creatinine will be recorded during treatment and on days 3 days thereafter.
SOFA Score:	The SOFA score (score able to describe organ dysfunction) will be measured at day 0 (pre-treatment, BL) and daily from day 1 to day 3. The actual values for each failure (P/F ratio, hypotension, diuresis or creatinine, bilirubin, PLT and GCS) and the SOFA score will be automatically calculate. The total score will be then recorded in the database.
Concomitant cares	The use of antibiotics, MV and CRRT will be recorded until day 28.
Hemodynamic variables:	HR, MAP, CI, SVI, SVRI, GEDVI, ITBVI and EVLWI will be measured at day 0 and daily from day 1 to day 3.
Blood Gas:	arterial pH, PaO ₂ , PaCO ₂ , FiO ₂ and P/F will be recorded at day 0 and daily from day 1 to day 3
Adverse events:	All adverse events, adverse events during treatment of PMX-20-R will be included in the database.
ICU length of stay (LOS) and premature conclusions:	Days of hospitalization in ICU and reasons for discharge

4. STATISTICAL ANALYSIS

4.1. Statistical information automatically updated and accessible to every user

Some information will be continuously processed and available in "real-time" for the users of the Database. Among these are the number of registered centers and the number of patients traced. Individual centers will be able to review and analyze all data for patients included in their center at all times until approval by the Clinical Monitor.

4.2. Statistical information available for SSC

The raw data will be analyzed each year by the SSC to monitor the use of the therapy in clinical practice, with particular reference to the variation of effectiveness of the treatment respect to:

- time of intervention,
- severity of the patient at the time of the first treatment,
- primitive pathology,
- level of endotoxemia (Assessment of Endotoxin Activity EAA™)

The efficacy of the treatment will be assessed by the same criteria used in the EUPHAS study:

- 20% decrease of vasopressor Dependency Index at 72 hours.
- A reduction of 3.5 points of Delta Sofa Score at 72 hours
- Renal function: significant improvement of urine output and/or frequency of CRRT
- Respiratory function: significant improvement in the oxygen metabolism, blood gases and/or MV-free days

- Improvement in the ICU length of stay and ICU-free days(meaning the real need for days of intensive care)
- patient prognosis.

In Italy over 600 polymyxin-B based cartridges are used each year (source Estor SpA), therefore it is predicted that if the EUPHAS 2 database could collect the data from 1/3 of these treatments, the data of 100 patients every year could be traced.

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