

PROTOCOL

Ministero della Salute – Direzione Generale della Ricerca Scientifica e Tecnologica

Form 1 - General information about the project

TITLE OF THE PROJECT (max 300 caratteri): Fenoldopam to prevent renal replacement therapy after cardiac surgery. A randomized controlled study performed in the Intensive Care Unit.

INSTITUTION ACCEPTING THE PROJECT: Fondazione Centro San Raffaele del Monte Tabor

SCIENTIFIC COORDINATOR:

Name: bove tiziana

Professional status: Medico Dirigente

Birth date and birth place : 10/05/1971, cosenza (CS)

E-mail address: bove.tiziana@hsr.it

Curriculum: CURRICULUM VITAE TIZIANA BOVE

Dr Bove Tiziana, is originally from Cosenza (May 10th 1971), Italy. She earned her degrees in Università Cattolica del Sacro Cuore, Rome and is currently Senior Anesthesiologist at Department of Cardiovascular Anesthesia and Intensive Care, Istituto Scientifico San Raffaele, Milan, Italy and Tutor of Anesthesia and Intensive Care at Vita-Salute University of Milano.

She is member of EACTA (European Association of Cardiothoracic Anaesthesiologists) and ITACTA (Italian Association of Cardiothoracic Anesthesiologists).

She is reviewer for international indexed Journals (Brazilian Journal of Medical and Biological Research, Minerva Anestesiologica)

Dr Bove has strong interest in Emergency Medicine. She worked as a Rescue Helicopter Doctor and for Europ Assistance for care and transport of critically ill expatriates in 2006/2007. She trained in PBLs (Paediatric Basic Life Support) in 2007, and ATLS in 2000.

Dr Bove has a strong interest in Intensive Care Medicine and attended numerous Ecocardiography and fibroscopy courses

Her special interest in renal protection allowed her to be invited to the 2007 ADQI (Acute Dialysis Quality Initiative) international consensus conference on acute renal failure in cardiac anesthesia and intensive care.

Strong clinical and research interests in cardiac anesthesia have resulted in numerous publications (18 indexed in pubmed), numerous invitations in national and international congresses and prizes as best paper in numerous national congresses. Among the most important published papers we evidence

--Bove T, Landoni G, Calabrò MG, Aletti G, Marino G, Cerchierini E, Crescenzi G, Zangrillo A. Renoprotective action of fenoldopam in high-risk patients undergoing cardiac surgery. A prospective, double-blind, randomised clinical trial. *Circulation* 2005;111:3230-5

--Landoni G, Biondi-Zoccai GG, Tumlin JA, Bove T, De Luca M, Calabrò MG, Ranucci M, Zangrillo A. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. *Am J Kidney Dis.* 2007;49:56-68.

--Bove T, Calabrò MG, Landoni G, Aletti G, Marino G, Crescenzi G, Rosica C, Zangrillo A. The incidence and risk of acute renal failure after cardiac surgery. *J Cardiothorac Vasc Anesth.* 2004;18:442-5

--Zangrillo A, Landoni G, Fumagalli L, Bove T, Bellotti F, Sottocorna O, Roberti A, Marino G. Methicillin-resistant *Staphylococcus* species in a cardiac surgical intensive care unit: a 5-year experience. *J Cardiothorac Vasc Anesth.* 2006;20:31-7

--Ranucci M, Soro G, Barzagli N, Locatelli A, Giordano G, Vavassori A, Manzato A, Melchiorri C, Bove T, uliano G, Uslenghi MF. Fenoldopam prophylaxis of postoperative acute renal failure in high-risk cardiac surgery patients *Ann Thorac Surg* 2004 78(4):1332-7

--Crescenzi G, Rosica C, Bove T, Landoni G, La penna E, Zangrillo A: Dilated coronary sinus and a ring structure between the left atrial appendage and the left superior pulmonary vein. *J Cardiothorac Vasc Anesth* 2007 Oct;5(21):761-762

--Landoni G, Bove T, Crivellari M, Poli D, Fochi O, Marchetti C, Romano A, Marino G, Zangrillo A: Acute renal failure after isolated CABG surgery: six years of experience. *Minerva Anestesiol.* 2007 Nov;73(11):559-565

RESEARCH TYPE: Ricerca Valutativa

LIST OF PARTICIPATING UNITS (UNITÀ OPERATIVE COINVOLTE): Name of the Institutions and of their Legal Representative (if needed an attachment should be added)

- Azienda Ospedaliera San Giovanni Battista Molinette di Torino , Galanzino Giuseppe
- Azienda Ospedaliera Universitaria Pisana , Contini Vairo
- Fondazione Centro San Raffaele del Monte Tabor , Verzè Luigi Maria
- Ospedale Papardo di Messina , Sirna Gaetano
- Ospedale Regionale di Treviso , Macagni Crescentina
- Policlinico Le Scotte di Siena , Tomassini Rinaldo
- Policlinico Sant'Orsola Malpighi , Cavina Augusto
- Spedali Civili di Brescia , Maggi Fausto

FORM 2 – DESCRIPTION OF THE PROJECT (SUMMARY OF THE ACTIVITIES OF ALL THE PARTICIPATING UNITS

WHAT IS ALREADY KNOWN ON THE SUBJECT (INCLUDE THREE RELEVANT REFERENCES IN PEER REVIEWED JOURNAL) (MAX 20 LINES)

A recent meta-analysis of randomised controlled studies suggested that fenoldopam reduces the need for renal replacement therapy (RRT) and mortality in critically ill patients with or at risk for acute kidney injury (AKI) [1]. These results were confirmed in the specific setting of cardiovascular surgery [2].

Perioperative renal function impairment is associated with significant in-hospital and long-term morbidity and mortality, as well as prolonged hospital stay [3].

Fenoldopam is a benzazepine derivative with selective postsynaptic dopamine-1 (DA-1) receptor agonist properties.

Fenoldopam has recently demonstrated nephroprotective properties in critically ill patients or those undergoing major surgery. A meta-analysis [1] of 16 randomized clinical trials (RCTs) including 1290 patients (622 receiving fenoldopam and 668 placebo or best available treatment, mostly low dose dopamine) was recently performed. Five trials were performed in cardiac surgery, 3 in vascular surgery, 2 in liver and 1 in renal transplants while 5 studies were performed in ICU either in selected patients with sepsis (2 studies) or in the overall ICU population. Fenoldopam dosage varied across studies, being always >0.025 $\mu\text{g}/\text{kg}/\text{min}$ and most often 0.1 $\mu\text{g}/\text{kg}/\text{min}$, reaching 0.3 $\mu\text{g}/\text{kg}/\text{min}$ in a single study. All but two studies had a >12 hours fenoldopam infusion, with 8 studies reporting >2 days infusion (median duration 48 hours). Overall analysis showed that, in comparison to best medical therapy, fenoldopam usage reduced the risk of RRT (34/525 [6.5%] in the fenoldopam group vs. 59/569 [10.4%] in the control arm, OR=0.54 [0.34-0.84], $p=0.007$), and all-cause mortality (81/537 [15.1%] vs. 110/581 [18.9%], OR=0.64 [0.45-0.91], $p=0.01$), as well as AKI (84/525 [16.0%] vs. 161/569 [28.3%], OR=0.43 [0.32-0.59], $p<0.001$).

In a second meta-analysis [2] 13 clinical studies comparing fenoldopam to placebo or usual care were included. The studies included 1059 patients (528 received fenoldopam and 531 placebo or best available treatment). Four trials were performed in vascular surgery and 9 in cardiac surgery.

Overall analysis showed that, in comparison to best medical therapy, fenoldopam was associated with significant reductions in the rates of all major endpoints. Specifically, fenoldopam usage reduced the risk of RRT (30/528 [5.7%] in the fenoldopam group vs. 71/531 [13.4%] in the control arm (OR=0.37 [0.23-0.59], p for effect <0.001 , number needed to treat=13) and of in-hospital death (28/501 [5.6%] in the fenoldopam group vs. 55/503 [10.9%] in the control arm (OR=0.46 [0.29-0.75], p for effect = 0.02 number needed to treat=19).

To confirm the promising results of the two recent meta-analysis above described [1,2] a large multicentre randomized controlled study will enrol patients who will develop AKI after cardiac surgery (50% postoperative increase in serum creatinine). Fenoldopam will be administered at a starting dose of 0.1 $\text{mcg}/\text{kg}/\text{min}$ (ranging from 0.025 to 0.3 $\text{mcg}/\text{kg}/\text{min}$) for 96 hours and compared in a double blind randomized fashion to placebo (normosaline).

1. Landoni G, Biondi-Zoccai GGL, Tumlin JA, Bove T, De Luca M, Calabrò MG, Ranucci M, Zangrillo A. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. *Am J Kidney Dis*. 2007 Jan; 49(1): 56-68.

2. Landoni G, MD, Biondi-Zoccai GGL, MD, Marino G, MD, Bove T, MD, Fochi O, MD, Maj G, MD, Calabrò MG, MD, Sheiban I, MD, Tumlin JA, Marco Ranucci M, MD and Zangrillo A, MD. Fenoldopam Reduces the Need for Renal Replacement Therapy and In-Hospital Death in Cardiovascular Surgery: A Meta-Analysis. *J Cardiothorac Vasc Anesth*. 2008;22:27-33.

3. Bove T, Calabrò MG, Landoni G, Aletti G, Marino G, Crescenzi G et al. The incidence and risk of acute renal failure after cardiac surgery. *J Cardiothorac Vasc Anesth.* 2004;18:442-5.

WHAT THE PROJECT ADDS TO THE INFORMATION ALREADY AVAILABLE (MAX 10 LINES)

The aim of this randomised, double blind study is to confirm the promising results of the above cited meta-analysis and to add evidence based medicine to the supposed renal protective properties of fenoldopam in critically ill patients.

30.000 cardiac surgical interventions are performed in Italy every year (and 1.000.000 in the world). Since acute renal failure develops in 2-10% of this population, up to 3000 patients in Italy (100.000 in the world) could benefit yearly from the results of this study.

The drug, according to a recent meta-analysis (Landoni G. et al. *Am J Kidney Dis.* 2007;49:56-68) would also be useful in all critically ill patients with or at risk for acute renal dysfunction.

Improved outcome of critically ill patients would be the most relevant implication of this study.

Reduction in cost per patient will be striking, since acute renal failure and renal replacement therapy prolong intensive care and hospital stay.

DETAILED DESCRIPTION OF THE PROJECT'S MAIN AND SECONDARY OBJECTIVE(S) (max 40 lines)

This large randomised double blind controlled study would enroll those patients who will develop an initial acute kidney injury after cardiac surgery (50% postoperative increase in serum creatinine).

Fenoldopam will be administered at a starting dose of 0.1 ug/kg/min (ranging from 0.025 to 0.3 ug/kg/min) for 96 hours and compared in a double blind randomised fashion to placebo (normosaline)

The study is powered to detect a reduction of the need of RENAL REPLACEMENT THERAPY (MAJOR END POINT) from 10% to 5%.(continuous venous venous ultrafiltration or haemodialysis, according to centre guidelines and protocols)

Renal replacement therapy after cardiac surgery is associated to an elevated mortality rate (up to 60%) despite improvements in intensive care and dialytic technology and in this study we expect to find important implications in hospital mortality (reduction from 5% to 2.5%) as well.

SECONDARY END POINTS will be represented by

--mortality (hospital mortality and telephone follow up at 30 days and at 1 year)

--time on mechanical ventilation (hours)

--length of intensive care and hospital stay (days)

--peak serum creatinine (mg/dl)

--acute renal failure (following the R.I.F.L.E. score definition)

Transfer out of the intensive care unit will be performed with SpO₂ 94% or greater at an FiO₂ of 0.5 or less by facemask, adequate cardiac stability with no hemodynamically significant arrhythmias, chest tube drainage less than 50 ml/h, urine output greater than 0.5 ml/kg/h, no intravenous inotropic or vasopressor therapy in excess of dopamine 5 ug/kg/min, and no seizure activity.

Criteria for hospital discharge will be hemodynamic and cardiac rhythm stability, the presence of clean and dry incisions, an afebrile condition, normal bowel movement, and independent ambulation and feeding.

METHODS

SPECIFY: (whenever applicable) a) Patients/population; b) Intervention(s)/Analytical procedures; c) Indicator(s); d) Study design; e) Statistical analysis (MAX 2 PAGES)

STUDY DESIGN

Multicentre, double blind, randomised controlled study on clinically relevant end-points (renal replacement therapy) in patients admitted in Intensive Care Unit following cardiac surgery.

STUDY POPULATION

Patients undergoing cardiac surgery (most of them are elderly) will sign a written informed consent and will be included in the protocol only if they will develop an initial acute kidney injury with respect to baseline (50% postoperative increase in serum creatinine or oliguria).

Fenoldopam will be administered at a starting dose of 0.1 ug/kg/min (ranging from 0.025 to 0.3 ug/kg/min) for 96 hours and compared in a double blind randomised fashion to placebo (normosaline)

CLINICAL SETTING WHERE THE STUDY WILL BE CONDUCTED

Cardiac Surgery Intensive Care Units (ICU) of numerous Italian Teaching Hospitals.

The follow up will be performed at Hospital discharge (clinical follow up), at 30 days and at 1 year (by phone contact with the patient, his/her physician, or direct visit) after the operation.

The study will start after the ethical committee approval. Consecutive patients who will sign the written informed consent will be enrolled over a 2 years period if they will develop an initial acute kidney injury after cardiac surgery.

INCLUSION CRITERIA

--written consent

--age >18 years

--acute renal injury defined as "R" of the R.I.F.L.E. score (50% postoperative increase in serum creatinine or diuresis <0,5 ml/kg/h for 6 hours)

--the patient is in Intensive Care Unit, following cardiac surgery, at the moment of randomisation.

EXCLUSION CRITERIA

-patient refusal

-previous unusual response to fenoldopam

-glaucoma

-expected stay in Intensive Care Unit less than 24 hours at the moment of randomisation

-renal replacement therapy already started or planned) before randomization

-do not resuscitate patient

-inclusion in other randomised controlled studies in the previous 30 days

-administration of fenoldopam in the last 30 days

-preoperative renal replacent therapy or dialysis

The study group will receive fenoldopam, administered at a starting dose of 0.1 ug/kg/min (ranging from 0.025 to 0.3 ug/ kg/min) for 96 hours and compared in a double blind randomised fashion to placebo (normosaline)

Five doses of the study drug could be used

0.025 ug/kg/min

0.05 ug/kg/min

0.1 ug/kg/min

0.2 ug/kg/min

0.3 ug/kg/min

The higher doses will be used after MAP>70 mmHg (or > 80 mmHg in patients known for hypertension) will be obtained for at least 30 minutes.

Lower doses will be used after MAP < 60mmHg (or <70 mmHg in patients known for hypertension) will be noted.

The treatment will last for 96 hours.

Early interruption will be performed if

--the patient will be discharged to the main ward (outside the Intensive Care Unit)

--adverse reactions will ensue.

Fluids, inotropic drugs and vasoconstrictors administrations will be managed by the on duty physician and will not influence the administration of the study drug.

Since the renal protective effects of fenoldopam seems to be related to the dose of administration it is suggested to maintain the dose of the study drug > or equal to 0.1 ug/kg/min.

Safety

The drug is safe and has been used as an antihypertensive drug in clinical practice for more than 15 years. We will probably observe more hypotensive episodes in the treatment group but it is not a problem to manage these episodes in the Intensive Care Units through i.v. fluids or drugs administrations as per on duty-physician

Primary end-point

The study is powered to detect a reduction of the need of RENAL REPLACEMENT THERAPY (MAJOR END POINT) from 10% to 5%.(continuous venous venous ultrafiltration or haemodialysis, according to centre guidelines and protocols)

Renal replacement therapy after cardiac surgery is associated to an elevated mortality rate (up to 60%) despite improvements in intensive care and dialytic technology and in this study we expect to find important implications in hospital mortality (reduction from 5% to 2.5%) as well.

Secondary end-points

SECONDARY END POINTS will be represented by

--mortality (hospital mortality and telephone follow up at 30 days and at 1 year)

--time on mechanical ventilations (hours)

--length of intensive care and hospital stay (days)

--peak serum creatinine (mg/dl)

--acute renal failure (following the R.I.F.L.E. score definition)

SAMPLE SIZE ESTIMATES

Sample-size calculation is based on a two-sided alpha error of 0.05 and 80% power. On the basis of recent literature and of our experience we anticipate a 10% of patients with renal replacement therapy in the control group and 5% of patients in the treatment group. We calculate that we will need a sample size of 435 patients per group. However, we plan to randomly select 500 patients in order to take into account possible protocol deviations. All 1000 patients will be analysed according to the intention-to-treat principle, beginning immediately after randomization.

The expected 50% reduction of major complications is in accordance with the results of the above cited meta-analysis 34/525 [6.5%] in the fenoldopam group vs. 59/569 [10.4%] in the control arm in the critically ill patients and 30/528 [5.7%] in the fenoldopam group vs. 71/531 [13.4%] in the control arm (OR=0.37 [0.23-0.59], p for effect <0.001, p for heterogeneity =0.51, I²=0%, number needed to treat=13 in the selected population of patients undergoing cardiovascular surgery.

Also the 10% incidence of renal replacement therapy in this population is in accordance to the above cited meta-analysis.

RANDOMIZATION

Subjects will be allocated according to a centralized randomisation derived from a computer-generated list of random number (in a sealed opaque envelope) that will be available only shortly before the preparation of the study drug. Two ml of fenoldopam (corlopam 20 mg/ 2ml) or placebo (normosaline) will be diluted in 100 ml of normosaline. The randomisation, performed at the last available moment, will reduce most biases together with the double blindness of the study. Data will be collected by trained observers who will not participate in patient care and will be blinded to the anaesthetic regimen.

All case report form will be monitored by medical specialists not directly involved in patient care, outsourced to a dedicated contract research organization (Associazione Endovasculare Onlus [AEO], Rome, Italy; <http://www.endovascularonlus.org>).

STATISTICAL ANALYSIS

A dedicated contract research organization (Associazione Endovasculare Onlus [AEO], Rome, Italy; <http://www.endovascularonlus.org>), not involved in patient management, will provide independent consultancy for data quality checking and statistical analysis, and will be responsible for the statistical analysis. Data will be stored electronically and analyzed by means of the Epi Info 2002 (CDC), SPSS 11.0 (SPSS), and STATA 9.0 (STATA) softwares, when appropriate. All data analysis will be carried out according to a pre-established intention-to-treat analysis plan.

We planned to perform two ad-interim analysis. If $p < 0.005$ after enrolling 250 patients or $p < 0.014$ after enrolling 500 patients the study will be interrupted.

TIMING

The study will be concluded within 2 years after the first randomization. The work in progress will be checked monthly. The final report will be provided 2 months after randomizing the last patient.

MONITORING OF THE STUDY

A dedicated and independent contract research organization (Associazione Endovascolare Onlus [AEO], Rome, Italy; <http://www.endovascularonlus.org>) will provide independent clinical monitors to verify adherence to required clinical trial procedures and confirm accurate collection of data. The monitors will follow the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines.

GENERAL TRANSFERIBILITY AND POTENTIAL IMPACT OF RESULTS (max 1/2 page)

The aim of this randomised, double blind study is to confirm the promising results of the above cited meta-analysis and to add evidence based medicine to the hypothesized renal protective properties of fenoldopam in critically patients.

The results will be transferred to the national and international community through

- a paper with the study design published in a national paper
- an abstract to a national and international congress with the preliminary result
- a paper on an international journal with the final results of this trial

We'll also organize a specific congress to illustrate the results of this trial.

30.000 cardiac surgical interventions are performed in Italy every year (and 1.000.000 in the world). Since acute renal failure develops in 2-10% of this population, up to 3000 patients in Italy (100.000 in the world) could benefit yearly from the results of this study.

The drug, according to a recent meta-analysis (Landoni G. et al. Am J Kidney Dis. 2007;49:56-68) would also be useful in all critically ill patients with or at risk for acute renal dysfunction.

Improved survival of critically ill patients would be the most relevant implication of this study.

Reduction in cost per patient will be striking, since acute renal failure and renal replacement therapy prolong intensive care and hospital stay.

OUTPUT(S) OF THE PROJECT (max 1/2 PAGE)

(DESCRIBE THE OUTPUTS THAT THE PROJECT WILL PRODUCE SPECIFYING WHEN - DURING THE PROJECT - THEY WILL BECOME AVAILABLE Example(s) of output: ANIMAL MODELS, METHODOLOGIC WORKPACKAGES, OTHER DELIVERABLES

The results will be transferred to the national and international community through

- a paper with the study design published in a national paper
- an abstract to a national and international congress with the preliminary result
- a paper on an international journal with the final results of this trial

We'll also organize a specific congress to illustrate the results of this trial.

MILESTONES ALONGSIDE THE PROJECT

(LIST UP TO TEN MILESTONES WITH RELEVANT RESULTS EXPECTED DURING THE PROJECT) (MAX 1 PAGE)

This question is not pertinent in a double blind randomised controlled study.

We'll perform two ad interim ad analysis after enrolling at 250 and 500 patient, but the results of the analysis will be blinded.

If the donor (Ministry of Health) is willing to have other kinds of endpoints such as the overall mortality after one year of enrolment and its correlation to the number of surgery/per centre we'll perform these analysis.

Furthermore we will

- publish a paper with the study design in a national paper
- present an abstract to a national and international congress with the study preliminary result after completing the trial
- publish a paper on an international journal with the final results of this trial

TIMETABLE OF THE PROJECT

See attached file