Clinical study protocol

Protocol Title:	A phase 4, single-centered, parallel-group, randomized, triple-blind, placebo-controlled study to compare the effects of pretreatment H_1 and H_2 antihistamines vs. placebo on changes in systemic arterial pressure following protamine administration in patients after cardiopulmonary bypass (CPB).
Protocol Identifier:	NCT03583567 (available online at clinicaltrials.gov)
Phase:	4
Investigational Product:	H_1 (chlorpheniramine) and H_2 (ranitidine) antihistamine injection
Indication:	Prevention of protamine reactions
Sponsor:	Mahidol University (Grant no.
Original Protocol:	July 11, 2018

Study Description

Brief Summary:

Protamine remains the anticoagulant of choice for cardiopulmonary bypass (CPB). The process of protamine neutralization of heparin came with the side effects sometimes; it can be life threatening or fetal reaction. The adverse cardiopulmonary response of protamine has been observed during entire history of clinical cardiac surgery. The true mechanism reaction is difficult to defined and the complexity of the clinical situation The classification of protamine reaction has been divided in to main 3 types (transient systemic hypotension secondary to rapid administration, anaphylactic and anaphylactoid reaction and catastrophic pulmonary vasoconstriction.

The reaction from pharmacologic histamine release is the most common type of reaction. Protamine was believed to induce hypotension by this mechanism, and it was demonstrated to release histamine by degranulation of isolated mast cells From the hypothesis that the systemic hypotension cause by the released of histamine. The investigators will measure the serum tryptase which is the enzyme that released from degranulation of human mast cell. Comparing the serum tryptase level of the patient at baseline, 30 min and 60 min after protamine was given.

Therefore, the hypothesis of this study is administrating of H1 and H2 blocker helps attenuate the drop in MAP after protamine is given.

Condition or disease	Intervention/Treatment	Phase
Protamine adverse reaction	Drug: Chlorpheniramine and ranitidine Drug: 0.9% Normal saline	Phase 4

Study Design

Study Type	Interventional (Clinical Trial)
Actual Enrollment	40 participants
Allocation	Randomized
Intervention Model	Parallel Assignment
Masking	Quadruple (Participant, Care provider, Investigator, Outcomes Assessors)
Masking Description	Normal saline will be used as placebo in the control group
Primary Purpose	Prevention
Official Title	A Randomized Controlled Study Comparing the Prophylactic Effect of histamine1 and Histamine 2 Receptor Blocker in Prevention Systolic Hypotension After Protamine Administration in Cardiac Patient Having Cardiopulmonary Bypass
Actual study start date	September 5, 2018
Study objectives	
Primary objectives	To compare systemic arterial pressure changes after protamine administration between pre-treatment H1 and H2 antihistmines and normal saline
Secondary objectives	To compare serial serum tryptase after protamine administration between pre-treatment H1 and H2 antihistmines and normal saline To compare inotropic and vasopressor support doses after protamine administration
Study Endpoints	The patients are transferred out of the operating room

Arms and interventions

Arm	Intervention/treatment
Placebo Comparator: 0.9% Normal Saline Syringe No 1 contains normal saline 1 mL Syringe No 2 contains normal saline 2 mL	Drug: 0.9% Normal Saline Patients will receive normal saline as placebo
Experimental: Chlorpheniramine and ranitidine Syringe No 1 contain chlorpheniramine 10 mg (1 mL) Syringe No 2 contain ranitidine 50 mg (2 mL)	Drug: Chlorpheniramine and ranitidine Patients will receive intravenous chlorpheniramine and ranitidine prior to protamine

All patients in both groups will receive standardized care for patients undergoing open cardiac surgery with CPB. Preoperative visits will be done the day before surgery by the anesthesia team responsible for patient care. The patients will be randomly allocated into two groups and receive intervention according to their group allocation.

In the operating room, standard noninvasive monitors will be placed and midazolam 1 mg and dexmedetomidine 50 mcg will be given before arterial line insertion. Anesthesia will be induced with propofol 1-2 mg/kg, fentanyl 1-2 mcg/kg, and cis-atracurium 0.02 mg/kg to facilitate intubation. Central venous catheter, urinary catheter, and nasopharyngeal temperature probe will be placed after induction. Anesthesia will be maintained with 1 – 2% sevoflurane in a mixture of air/O2, fentanyl 1 mcg/kg/hr, and cis-atracurium 0.03 mg/kg every 30 minutes throughout the operations. All medications that potentially trigger histamine release will be avoided. Normocarbia ($PaCO_2$ of 35 – 45 mmHg) will be kept through out the procedure. Systolic blood pressure (SBP) and mean arterial pressure (MAP) will be maintained within 20% of the patient's baseline before CPB is established.

Heparin 3 mg/kg (300 U/kg) will be given before aortic cannulation to maintain activated clotting time (ACT) more than 480 seconds before CPB initiation and throughout CPB. Management during CPB is based on the institutional standard. The bypass circuit is primed with acetate ringer's solution 1800 mL, heparin 5000 U, sodium bicarbonate 44.6 mEq, 20% mannitol 0.5 g/kg, and 20% albumin 100 mL. Cardiopulmonary bypass is performed using a non-occlusive roller pump and non-pulsatile flow is maintained between 2.0 – 2.4 L/min/m^{-2}

with a target perfusion pressure of 50 – 80 mmHg. Intermittent bolus of norepinephrine will be administered to maintain perfusion pressure as needed if the target non-pulsatile flow has been achieved. Mild hypothermia (32ºc – 34 ºc) will be instituted along with alpha-stat pH management. St. Thomas cardioplegia is used. The blood cardioplegia will be mixed at a 4:1 blood to crystalloid ratio and will be delivered antegrade or retrograde until asystole.

Study drug will be prepared by one of the authors who are not involve in patient care and given according to group allocation immediately after separation from CPB. Each syringe will be labeled as 'study drug'. Five minutes after the study drugs are given, 3 mg/kg of protamine will be given in 5 minutes infusion via peripheral line. Types and doses of inotropic and vasopressor drugs for hemodynamic support after separation from CPB will be selected based on the attending anesthesiologist's judgment to maintain MAP within 20% of baseline. Surgeons will be asked to minimize surgical manipulation of the heart after the starting of protamine infusion to avoid abrupt hemodynamic changes from surgical factors. Decannulation will be performed once half of the dose of the protamine has been given. After the procedures end, all patients will be transferred to the cardiac surgical intensive care unit intubated.

Outcome Measures

Primary Outcome Measures:

Blood pressure (Time Frame: 37 minutes)

Systolic and diastolic blood pressure will be recorded every minute since the start of protamine infusion (in 7 minutes) til 30 minutes after infusion.

Secondary Outcome Measures:

Serum tryptase (Time Frame: 60 minutes)

Serum tryptase will be measured before the administration of protamine and at 30 minutes and 60 minutes after protamine

Vasoactive-Inotropic Score (VIS) (20) at each time point as vital signs are recorded (Time Frame: 37 minutes)

VIS = dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 100 x epinephrine dose (mcg/kg/min) + 50 x levosimendan dose (mcg/kg/min) + 10 x milrinone dose

(mcg/kg/min) + 10,000 x vasopressin dose (units/kg/min) + 100 x norepinephrine dose (mcg/kg/min).

Eligibility Criteria

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- ASA physical status 1-3
- Schedule for open heart surgery with cardiopulmonary bypass (CPB)

Exclusion Criteria:

- History of allergy to the study drugs or protamine
- History of previous cardiac surgery or received protamine
- History of diabetes with insulin therapy

Statistical methods

Analysis population includes all randomized patients. Patients will be analyzed according to their group randomization. Study data will be collected and managed using REDCap® electronic data capture tools hosted at Mahidol University.

Continuous data were compared using Student's t-test or Mann-Whiney U test as appropriate The effect of protamine administration on changes in systolic and mean arterial pressure during the first 35 minutes (20-time points) after protamine administration will be compared using Generalized Estimating Equations (GEE) with exchangeable correlation structure. Effects of protamine were reported as crude and adjusted mean difference, 95% CI, and p-value.

Contacts and Locations

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More Information

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Plan to Share IPD:	No
Studies a U.S. FDA-regulated Drug Product:	No
Studies a U.S. FDA-regulated Device Product:	No

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