Official Title: Role of Levothyroxine Supplementation in Delayed Recovery Following Cardiac Surgery

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Protocol Of A Paper For Partial Fulfilment Of Research In Anesthesia, ICU and pain management

The title: Role of Levothyroxine supplementation in delayed recovery following cardiac surgery.

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1. INTRODUCTION/ REVIEW (Maximum 1000 words) *"References are needed"*

Research indicates that hypothyroidism decreases heart contractility, reduces stroke volume and rate, affects the vascular endothelium, and increases the risk of atherosclerosis, systemic vascular resistance, hypertension [1], atherogenic lipid profile, and coagulation abnormality [2].

Hypothyroidism was reported to be strongly related to cardiovascular disease, respiratory complications, neurological complications, and a significant difference in ventilator weaning time [3].

Severe thyroid dysfunction is related to muscle relaxation and lead to respiratory muscle depression and disturbed conscious level.[3]

Surgical stress of cardiac surgery might be followed by a prolonged recovery process and cardiac dysfunction [3].

The exact physiology of thyroid disease and the relationship with post cardiac surgery remain unclear. Thus far, large-scale clinical statistical analysis evidence on the complication rate and long-term mortality is lacking. Current important prognostic assessment tools such as EuroSCORE II [4], and Society of Thoracic Surgeons (STS) score [5] do not include thyroid function assessment, even though it has a significant impact on the metabolic, cardiovascular, and circulation system.

2. AIM/ OBJECTIVES (Maximum 300 words)

The primary aim of this study is to investigate the effect of supplementation of oral levothyroxine in delayed recovery patients post cardiac surgery.

3. METHODOLOGY:

Patients and Methods/ Subjects and Methods/ Material and Methods (Maximum 1000 words) *"References may be needed"*

This study is a prospective, randomized controlled trial that will study the postoperative clinical outcomes of levothyroxine supplementation in delayed recovery or prolonged ventilation patients post cardiac surgery.

Randomization will be performed using a computer-generated randomization sequence and allocation concealment to be maintained all through the time of procedure, by using opaque, numbered, and sealed envelopes.

The study protocol will receive ethical approval from the Research Ethical Committee/ Institutional Review Boards, Faculty of Medicine Ain Shams University.

Informed consent will be obtained from each patient before patients' allocation.

Type of the study: prospective randomized clinical trial study protocol**.**

Study Setting: The operating theaters and ICU of Cardiothoracic institute of Ain Shams University Hospitals.

Study period: one year.

Sample Size:

Using PASS 15 program for sample size calculation, setting power at 80% and alpha error at 0.05, it is estimated that sample size of 25 patients per group total 50 patients can detect an effect size .80 or the difference between two groups regarding different qualitative outcome measures using two-sized a z test

Study population:

Inclusion criteria:

- Age group: Adult patients from age of 45 to70 years.

Hypothyroidism was reported to be strongly related to cardiovascular disease, respiratory complications, neurological complications, and a significant difference in ventilator weaning time [3].

- Sex: Both sexes
- Elective, urgent and emergency open heart surgeries.

Exclusion criteria:

- Patients refuse to give informed consent.
- Patient younger than 45 years old, older than 70 years old.

- Off pump patients.
- Patients known hypothyroidism on levothyroxine supplementation.
- Patients known hyperthyroidism on Carbimazole.

Sampling method:

Patients will be randomly allocated by computer generated randomization into two groups A and B:

- **Group A (Study group):** patients receiving oral supplementation of levothyroxine.

- **Group B (Control):** patients receiving Placebo drug.

Anesthetic management:

Full standard preoperative assessment for cardiac surgery will be done for all patients included in the study before planned procedures.

Premedication will be given according to standard protocol in cardiac anesthesia. Routine monitoring included a five-lead electrocardiogram, pulse oximeter and invasive blood pressure. Anesthesia will be induced with midazolam 0.02mg/kg and fentanyl 2-5 microgram /kg and muscle relaxation were achieved cisatracurium 0.15 mg/kg intravenous. After tracheal intubation, central venous line and TEE inserted, then anesthesia will be maintained throughout the procedure with morphin20 microgram/kg /min, cisatracurium 2mg/kg/min and sevoflurane 2%. Ventilation will be adjusted to maintain end-tidal carbon dioxide in the range of 30-40 mmHg.

On ICU arrival all patients will be subjected to standardized management as per institutional protocols. Patients who show signs of delayed recovery defined as either prolonged ventilation for 48 hours or delayed conscious level recovery for 48 hours despite exclusion of muscle relaxants and/or sedative drugs. Those patients will undergo CT brain, CT chest and neurological examination to exclude structural damage as per institutional protocols. Also, metabolic profile screening including full kidney function, full liver function, electrolyte and thyroid profile (TSH, free T3, free T4) to exclude correctable metabolic abnormalities.

Patients then divided into two groups: group A will receive levothyroxine via Ryle, dose of 25 to 50 ug/ day according to BMI, while group B will receive placebo in form of inert starch tablet.

Daily assessment of conscious level according to Glasgow Coma Scale (GCS) and spontaneous breathing trial by ICU consultant till ICU discharge.

Assessment of thyroid profile (free T3, free T4, TSH) before hospital discharge.

Endpoints of the study:

Primary end point:

1. Improvement of Glasgow coma scale and spontaneous breathing trial before ICU discharge.

Secondary end points:

1. Total ventilation time.
2. Total ICU stay.
3. Total hospital stay.
4. Total amount of inotropic support.
5. Improvement of cardiac function by echocardiography.

Ethical considerations:

The study protocol will receive ethical approval from the Research Ethical Committee, Faculty of Medicine Ain Shams University.
Informed consent will be obtained from each patient before patients' allocation.

Sample Size Calculation

Using PASS 15.0 (NCSS LLC), detecting an effect size of 0.80 in GCS change (α = 0.05, power = 80%) required 25 patients per arm. To ensure adequate power for secondary endpoints and allow for dropouts, we enrolled 35 patients per group (total n = 70).

Statistical Analysis

Analyses adhered to the intention-to-treat principle. Continuous variables are reported as mean ± SD or median (IQR) and compared using Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables are expressed as counts (%) and compared by χ^2 or Fisher's exact test.

- **Primary analysis:** Linear mixed-effects regression modeled GCS trajectories over time, with group, time, and their interaction as fixed effects and patient as a random effect.
- **Time-to-event outcomes:** Kaplan–Meier curves and Cox proportional hazards models yielded hazard ratios (HRs) and 95% confidence intervals (CIs).
- **Mediation:** The Sobel test quantified the proportion of EF preservation attributable to changes in free T3.

- **Sensitivity and subgroup analyses:** Inverse probability weighting assessed robustness; prespecified subgroups included diabetes status and CPB duration > 200 minutes.

All tests were two-tailed with $\alpha < 0.05$. Statistical analyses were performed using R v4.3.1 with the lme4, lavaan, and survminer packages.

4. REFERENCES (Maximum 20 references)

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