STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Bisoprolol Versus Cognitive Behavioral Therapy on Cortisol, Blood Pressure, and Anxiety in Patients on Continuous Ambulatory Peritoneal Dialysis: A Pilot Quasi-Experimental Study

Item	Details
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Sponsor	Universitas Sebelas Maret, Surakarta, Indonesia
Study site	Dr. Moewardi General Hospital, Surakarta, Central Java, Indonesia
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This English document was prepared on 14 October 2026 for registration on ClinicalTrials.gov. It reproduces the study protocol approved by the Health Research Ethics Committee of Dr. Moewardi General Hospital (No. 1.230/IX/HREC/2022, 28 September 2022). The original protocol was written in Indonesian as part of the principal investigator's specialist thesis. This document does not contain names of research participants.

1. Background and rationale

Chronic kidney disease (CKD) is a major cause of death and health spending in Indonesia. Patients with stage 5 CKD need kidney replacement therapy. Continuous ambulatory peritoneal dialysis (CAPD) is one option. In Indonesia, only about 2% of patients on dialysis use CAPD.

Kidney failure and lifelong dialysis are chronic stressors. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis. The end product of this axis is cortisol. Stress also raises epinephrine and norepinephrine. These hormones bind beta-adrenergic receptors and activate the sympathetic nervous system.

Psychotherapy is one way to manage stress. Cognitive behavioral therapy (CBT) uses structured methods to change negative thoughts and unhelpful behaviors. Bisoprolol is a selective beta-1 adrenergic blocker. Beta-blockade may weaken the effects of stress hormones. Epinephrine can also stimulate cortisol secretion. Bisoprolol may therefore lower cortisol.

No earlier study has compared bisoprolol and psychotherapy on cortisol levels in patients on CAPD. This study was designed to fill this gap.

2. Objectives

2.1 General objectives

1. To assess the effect of bisoprolol on blood cortisol levels in patients with CKD on CAPD.
2. To assess the effect of psychotherapy on blood cortisol levels in patients with CKD on CAPD.
3. To compare the effects of psychotherapy and bisoprolol on blood cortisol levels in patients with CKD on CAPD.

2.2 Specific objectives

1. To measure blood cortisol levels in patients on CAPD who receive bisoprolol.
2. To measure blood cortisol levels in patients on CAPD who receive psychotherapy.

3. Hypotheses

1. Bisoprolol affects blood cortisol levels in patients with CKD on CAPD.
2. Psychotherapy affects blood cortisol levels in patients with CKD on CAPD.
3. The effects of psychotherapy and bisoprolol on blood cortisol levels differ in patients with CKD on CAPD.

4. Study design

This is a quasi-experimental study with a pre-test and post-test design in two parallel groups. One group receives psychotherapy. The other group receives bisoprolol. Each treatment lasts 30 days. Outcomes are measured before and after treatment. The study is open-label. Participants and investigators are not blinded.

5. Setting and study period

The study takes place at the Internal Medicine Outpatient Clinic (Division of Nephrology and Hypertension) and the Hemodialysis Unit of Dr. Moewardi General Hospital, Surakarta, Central Java, Indonesia. Data collection runs from November 2022 to March 2023, under research permit No. 045/10.567/2022 (valid 10 November 2022 to 9 March 2023).

6. Study population

- **Target population:** patients with chronic kidney failure on routine CAPD.

- **Source population:** patients with chronic kidney failure on routine dialysis follow-up at the Division of Nephrology and Hypertension, Dr. Moewardi General Hospital, Surakarta.

7. Eligibility criteria

7.1 Inclusion criteria

1. Patients with chronic kidney failure on CAPD.
2. Willing to take part, shown by signed informed consent.

7.2 Exclusion criteria

1. Use of drugs other than the routine drugs prescribed by the internal medicine clinic.
2. Previous psychotherapy.
3. Allergy to bisoprolol.
4. Bradycardia.
5. Severe illness.

7.3 Withdrawal (drop-out) criteria

1. Not following the agreed study procedures.
2. Cannot be contacted.
3. No longer willing to take part (withdrawal of consent).
4. Death during the study.

8. Sample size

Sample size was calculated with Federer's formula for experimental studies:

$$(t - 1)(r - 1) \geq 15$$

where t is the number of groups and r is the number of subjects per group. With $t = 2$, $(2 - 1)(r - 1) \geq 15$, so $r \geq 16$. The minimum sample is 16 subjects per group, or 32 in total. With an expected drop-out rate (f) of 10%, the corrected sample is $n' = n / (1 - f) = 32 / 0.9 = 35.6$, rounded to 36. The planned sample is therefore 36 subjects, with 18 in each group.

9. Sampling and group allocation

Patients who attend the clinic and meet the eligibility criteria are enrolled in sequence until the required number is reached. Enrolled patients are divided into two groups: Group 1 receives psychotherapy, and Group 2 receives bisoprolol.

10. Interventions

- **Group 1, psychotherapy:** individual cognitive behavioral therapy based on psychological principles. Sessions are given during routine clinic visits over 30 days.
- **Group 2, bisoprolol:** bisoprolol 5 mg orally once daily for 30 days.
- Patients in both groups continue their routine treatment from the internal medicine clinic.

11. Study variables and operational definitions

Independent variables: bisoprolol and psychotherapy. **Dependent variable:** blood cortisol level. **Secondary variables:** blood pressure, pulse rate, anxiety score, and sleep quality. **Potential confounders:** age, body mass index, sex, other comorbidities, and socioeconomic status.

Variable	Definition	Measurement	Unit	Scale
Bisoprolol	A selective beta-1 adrenergic blocker	Bisoprolol 5 mg per day for 30 days	–	Nominal
Psychotherapy	Individual interpersonal therapy based on psychological principles (cognitive behavioral therapy)	Given or not given	–	Nominal
Blood cortisol	Cortisol in venous blood, a biomarker of psychological stress	Morning venous blood sample, measured at Prodia clinical laboratory	µg/dL	Ratio
Systolic and diastolic blood pressure	Blood pressure measured at the clinic	Measured after rest	mmHg	Ratio
Pulse rate	Number of heart beats per minute	Measured after rest	beats/ min	Ratio
Anxiety score	Severity of anxiety symptoms	Standard anxiety rating scale	points	Interval
Sleep quality	Self-rated sleep quality over the past month	Pittsburgh Sleep Quality Index (PSQI), global score 0–21	points	Interval

12. Study procedures

1. Patients are screened against the eligibility criteria.
2. The investigator explains the aims, procedures, and benefits of the study. Patients who agree sign the informed consent form.
3. Baseline (pre-test): a morning venous blood sample is taken for cortisol. Blood pressure, pulse rate, and anxiety score are recorded.
4. Patients receive psychotherapy or bisoprolol for 30 days.
5. Day 30 (post-test): a morning venous blood sample is taken again for cortisol. Blood pressure, pulse rate, and anxiety score are recorded again. Sleep quality is assessed with the PSQI.
6. Data are checked, coded, and analyzed.

Cortisol is measured at the Prodia clinical laboratory.

Table 1. Schedule of assessments

Assessment	Screening	Baseline (day 0)	Day 30
Eligibility check and informed consent	X		
Blood cortisol (morning venous sample)		X	X
Blood pressure and pulse rate		X	X
Anxiety score		X	X

Assessment	Screening	Baseline (day 0)	Day 30
Pittsburgh Sleep Quality Index			X
Psychotherapy or bisoprolol		Day 1 to day 30	

13. Outcome measures

13.1 Primary outcome

- Change in blood cortisol level from baseline to day 30 (µg/dL).

13.2 Secondary outcomes

- Change in systolic blood pressure from baseline to day 30 (mmHg).
- Change in diastolic blood pressure from baseline to day 30 (mmHg).
- Change in pulse rate from baseline to day 30 (beats/min).
- Change in anxiety score from baseline to day 30 (points).
- PSQI global score (points).

14. Statistical analysis plan

14.1 Analysis population

All enrolled participants with available baseline and day-30 data for an outcome are included in the analysis of that outcome. Missing data are not imputed.

14.2 Descriptive statistics

Continuous data are shown as mean ± standard deviation, or as median and interquartile range if not normally distributed. Categorical data are shown as counts and percentages.

14.3 Normality

Normality is tested with the Shapiro-Wilk test in each group.

14.4 Baseline comparison

Baseline characteristics are compared between groups with the independent t-test or the Mann-Whitney U test. Sex distribution is compared with Fisher's exact test.

14.5 Primary analysis

The change in cortisol (day-30 value minus baseline value) is compared between the two groups. The independent t-test is used if the data are normally distributed. The Mann-Whitney U test is used if they are not.

14.6 Within-group analysis

Baseline and day-30 values within each group are compared with the paired t-test, or with the Wilcoxon signed-rank test for non-normal data.

14.7 Secondary outcomes

Secondary outcomes are analyzed in the same way as the primary outcome.

14.8 Significance and software

A two-sided p-value below 0.05 is considered significant. No adjustment is made for multiple comparisons. The analyses are exploratory. Data are analyzed with IBM SPSS Statistics version 25.0.

15. Ethical considerations

- The protocol was approved by the Health Research Ethics Committee of Dr. Moewardi General Hospital (No. 1.230/IX/HREC/2022, 28 September 2022).
- The study follows the Declaration of Helsinki.
- Each patient receives an explanation of the aims and benefits of the study before giving written informed consent.
- Participation is voluntary. Patients may withdraw at any time without any effect on their routine care.
- Participant data are coded. Names are not used in data analysis or reports. Data are kept by the study team and used only for this study.