Statistical Analysis Plan

Study objectives: The aim of this double-blind randomized study is to investigate the effect of dexmedetomidine on POD, ED, POCD incidence as well as on sleep quality and pain in the postoperative period in older adults (>65 years old) undergoing elective major orthopedic surgery.

The null hypothesis was that sedation with dexmedetomidine will be associated with lower incidence (10% decrease in POD) of POD and POCD and better sleep quality compared to propofol sedation.

Statistical Methodology

Outcome measures and assessments: Incidence of post-operative delirium and post-operative cognitive dysfunction (early & late), emergence delirium, sleep disturbances/sleep deterioration, acute and chronic pain

Post-operative delirium testing time windows: 8h postoperatively (± 1h) and every 12h (±2h) till 72h with intermediate assessments if needed (nurse and relatives screening – abnormal behavior identification)

Psychometric and sleep quality testing Time windows

Visit (target day)	Lower bound	Upper bound
Baseline (-1)	N/A	N/A
48 Hours (2^{nd} post - op day)	40 hours	56 hours
Month 3 (90)	80 days	100 days

Analysis populations: Patients scheduled for major orthopedic surgery of the lower limbs (total hip or knee replacement) under regional anesthesia sedated with propofol (control group) and dexmedetomidine (study group)

Statistical methods for primary and secondary outcomes: Descriptive statistics, chi-square tests, normality tests (both qualitative e.g. graphical distribution and Shapiro-Wilk), independent sample t-tests, Mann-Whitney U tests, binary logistic regression models, mixed ANOVAs and ANCOVAs.

Sample Size calculation: On a previous study of the Cretan population aged >65 years, an overall incidence of post-operative delirium at approximately 20% was identified(1). The same percentage was also identified in another study including only patients undergoing hip and knee replacement under spinal anesthesia(2). Based on these data power analysis

indicated a need for 120 patients per group for statistical significance at $p<0.05$ to detect a 10% decrease in delirium incidence.

Data handling: Data will be recorded in an anonymized-coded version for blinding and patient personal data privacy reasons.

Interim Analysis: Predefined interim analysis will be conducted by a independent investigator at 1/3 and 2/3 of the targeted sample size. The study will be stopped if a statistically important difference is shown between interventions ($p\leq0.001$) according to Haybittle-Peto rule and conditional power calculation is > 80% during interim analysis. Otherwise, study will be completed when calculated sample size is reached.

Handling of Missing, Unused, and Spurious Data: Patients with missing data will be excluded from the study.

Software: MS Excel and IBM SPSS will be used for data analysis.

Bibliography:

1. Papaioannou A, Fraidakis O, Michaloudis D, Balalis C, Askitopoulou H. The impact of the type of anaesthesia on cognitive status and delirium during the first postoperative days in elderly patients. Eur J Anaesthesiol . 2005 Jul;22(7):492–9. Available from: https://pubmed.ncbi.nlm.nih.gov/16045136/

2. Xie Z, Swain CA, Ward SAP, Zheng H, Dong Y, Sunder N, et al. Preoperative cerebrospinal fluid β-Amyloid/Tau ratio and postoperative delirium. Ann Clin Transl Neurol. 2014 May 1 1(5):319–28. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/acn3.58