Statistical analysis plan (SAP)

Regional or General Anesthesia for Delirium in Hip Fracture Surgery

ClinicalTrials.gov identifier : NCT02213380

1. Administrative Information

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2. Introduction

This document details the statistical analysis plan for the comparison of regional with general anaesthesia on postoperative delirium (RAGA-delirium) in the older patients undergoing hip fracture surgery. The clinical trial is registered at ClinicalTrials.gov (NCT02213380). One should also refer to the trial protocol paper[1].

2.1 Background and Rationale

Postoperative delirium is a common serious postoperative complication, especially in older people and is associated with increased mortality, morbidity, and healthcare costs[2,3]. General anaesthesia and regional anaesthesia are routinely administered during surgery in elderly people. The choice and use of general anaesthesia and regional anaesthesia are predominantly based on the anaesthetist, discussion with the patients and their cares.

There is no clear consensus on which anaesthesia is associated with less incidence of postoperative delirium for older patients. The long-term objective is to assess whether regional anaesthesia results in a lower incidence of postoperative delirium than general anaesthesia among older patients undergoing hip fracture surgery.

2.2 Objectives

This clinical trial is pragmatic, multicentre, prospective, parallel grouped, randomised controlled. The RAGA trial aims to determine whether different types of anaesthesia (regional anaesthesia vs general anaesthesia) given to older patients undergoing hip fracture surgery result in the equivalent incidence of postoperative delirium.

This will be met through meeting the following aims (as specified in the protocol):

- Aim 1: To assess whether there are differences in the incidence of postoperative delirium in different groups (by age, existing cognitive impairment, or preoperative delirium) between groups;

- Aim 2: To compare the subtypes, severity, and duration of postoperative delirium between the anaesthesia groups;
- Aim3: To describe the pain scores in the postoperative period either regional anaesthesia or general anaesthesia;
- Aim4: To compare the occurrence of non-delirium complications between the groups;
- Aim 5: Assessment of the length of hospital stay between groups;
- Aim 6: Assessment of the mortality during the hospital stay and the follow-up period after hospital admission between groups;
- Aim 7: Assessment of the cognitive and functional decline and quality of life on 30 days, 6 months, and 12 months after surgery between groups.
- Aim 8: To assess the cost-effectiveness of using regional anaesthesia compared to general anaesthesia in terms of total in-hospital costs and expenditure of anaesthesia.

3. Study Methods

3.1 Trial Design

This clinical trial is pragmatic, multicenter, prospective, parallel grouped, randomised controlled with cost-effective analysis. Participants will be randomised in a 1:1 ratio to regional anaesthesia or general anaesthesia.

3.2 Randomisation

Randomisation to regional anaesthesia or general anaesthesia is conducted in a 1:1 ratio, one day before surgery, using computer-generated assignment (web or telephone developed by the study data management provider).

3.3 Power and Sample Size

Based on the previously published incidence of postoperative delirium diagnosed using Confusion Assessment Method ranged from 28% to 50% in the elderly patients (age 65) during the hospital stay for hip fracture surgery, the observational studies in China estimated 3-day postoperative delirium incidences of 11.1%–23.3%.[4-6]Assuming postoperative delirium incidences in general anaesthesia OF 26% and a reduction of 30% postoperative delirium in RA, 441 patients should be needed for each group to give power (1-β) of 80% and the significance level of 5% (two-sided). With an estimated drop-out rate of 10%, a total of 1000 patients will be recruited from the nine clinical trial centers in China.

4. Statistical Principles

Statistical analysis will be conducted in accordance with the plan outlined in the SAP. Statistical analysis will abide by these general statistical principles below.

4.1 Confidence Intervals and p-values

All estimates of differences between groups would be presented with two-sided 95% confidence intervals unless otherwise stated. Statistical significance will be considered if $p<0.05$ (two-sided).

4.2 Modeling Principles

Intervention groups will be compared using a log-binomial regression model.

4.3 Multiple Comparisons

The primary outcome will be tested at 5% (two-sided) significance level. No corrections will be made for multiple comparisons, so intervals should not be used to infer treatment effects. As described in our research proposal, each comparison made will be hypothesis-driven and not hypothesis-generating.

4.4 Analysis Sets

4.4.1 Enrolled

The Enrolled set will include all patients who have provided informed consent and have been included in the study database.

4.4.2 Full Analysis Set

The Full Analysis Set (FAS) will be defined as all patients randomly assigned to a treatment group having at least one efficacy assessment after randomisation.

4.4.3 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPS) will include all randomised patients meeting the study eligibility criteria, at least one efficacy assessment after randomization. Patients who have one or more protocol deviations would be excluded.

4.5 Missing Data

In the primary outcome analysis, postoperative delirium, the missing values in Full Aanlaysi Set will not be imputed.

4.6 Analysis Populations

All analyses of primary and secondary outcomes, including safety outcomes, will be based on intention-to-treat. Participants would be analysed in the intervention group to which were randomised, and all participants shall be included whether or not they received the allocated intervention.

As a sensitivity analysis, a per-protocol analysis would also be carried out for the primary outcome and secondary outcomes.

5. Definition and Derived variables

5.1 Primary outcome

The primary outcome is the incidence of an episode of delirium during the first 7 postoperative days, assessed daily by the Confusion Assessment Method. An episode is defined if both acute onset and fluctuating course and inattention criteria were met, and one or both of either disorganised thinking or altered levels of consciousness criteria were met.

5.2 Secondary outcomes

Severity and Subtypes

The 13 items from Delirium Rating Scale-Revised-98 contribute to a severity score (items are scored zero to three, range from zero [no delirium] to 39 [maximum severity]) including two items which also define hyperactive (score $\geqslant 1$ on motor agitation), hypoactive (score $\geqslant 1$ on motor retardation), mixed motor (score $\geqslant 1$ on both motor items) or no motor (score=0 on both motor items) subtypes of delirium.

Visual analogue scale (VAS)

Pain scores are measured using VAS (ranges from 0 [no pain] to 100 [worst pain], assessed daily, over the seven days and the highest pain score will be reported as continuous data. The first three days' VAS also will be analysed by comparison between groups.

30-day mortality is all-cause mortality during 30 days post-surgery.

Length of hospital stay is calculated from the first post-operative day to discharge.

Costs of the anaesthetic procedure include the expenditure of anaesthesia; anaesthetic drug, and labour cost.

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Total in-hospital costs include the expenditure of anaesthesia, surgery, and hospitalisation.

5.3 Subgroups:

Pre-delirium is defined as whether patients had delirium before the intervention, using the Confusion Assessment Method on the day of admission.

Pre-existing dementia is defined by the Mini-Mental State Examination (MMSE) score with thresholds adjusted for educational levels.

- MMSE scores from 0 to 17 without educational experience/illiteracy;
- MMSE scores from 18 to 20 with an educational level less than primary education;
- MMSE scores from 21 to 22 with an educational level less than high school diploma;
- MMSE scores from 23 to 24 with an educational level less than a bachelor's degree.

Age is categorised by groups 65 to 80 years vs>80 years.

6. Trial Population

6.1 Recruitment

A flow diagram (as recommended by CONSORT) will be produced to describe the participant flow through each stage of the trial. The consort diagram will include the reasons for the loss of primary outcome data (Drop-outs and withdrawals) over the course of the trial.

6.2 Baseline Characteristics

Categorical data will be summarised by frequencies and percentages. Continuous data will be summarised by the number of responses, mean and standard deviation if deemed to be normally distributed, and the number of responses, median and interquartile range or total range if data appear skewed. Tests of statistical significance will not be undertaken, nor confidence intervals presented [7].

7. Statistical Analysis

7.1 Primary outcome:

The primary outcome is the incidence of postoperative delirium during 7 postoperative days, diagnosed with the Confusion Assessment Method, and will be a categorical variable.

7.2 Secondary outcome measures are as follows:

- The subtype, severity, and duration of delirium in 7 days after the surgery, diagnosed with the Delirium Rating Scale-Revised-98 and confusion Assessment Method, subtypes and duration of delirium are categorical variables, and severity score is a continuous variable;
- Duration of delirium, measured by days from the onset of delirium symptom to the resolution of symptoms, which is a continuous variable;
- The intensity of postoperative pain, measured with acute pain score in 7 days after the surgery using Visual Analogue Scale (VAS), which is a continuous variable;
- The occurrence of non-delirium in-hospital complications within 30 days after surgery, including chest infection, myocardial infarction, renal failure, gastrointestinal ileus, which is a categorical variable;
- Length of hospital stay, measured by the sum of inpatient days from admission to discharge, which is a continuous variable;
- Mortality during the hospital stay and during the follow-up period after hospital admission, which is a categorical variable;
- Incidence of delirium in the clinic or at the residence on 30-day, 6 months, 12 months after surgery, diagnosed with CAM, which is a categorical variable;
- Cognitive and functional decline on 30-day, 6 months, 12 months after surgery, diagnosed with Mini-Mental State Examination (MMSE) and Hospital Anxiety and Depression Scale, which is a categorical variable;
- Quality of life on 30 days, 6 months, 12 months after surgery, using 36-Item Short Form questionnaire, which is a categorical variable;

- Economic parameters, including total cost in hospital and expenditure for anesthesia and resource using costs, including equipment and disposables required for each anesthetic technique, which are the continuous variables.

8. Analysis Methods

8.1 Primary outcome

For the analysis of the primary outcome measure, the log binomial model will be used to generate relative risks (RR) along with 95% confidence intervals. Statistical significance of the treatment group variable will be determined through the examination of the associated chi-squared statistic.

8.2 Secondary outcomes (SO)

SO1: Frequency counts will be summarised by treatment group. RR and associated 95% CI will be calculated.

SO2: Duration of delirium will be summarised using basic descriptive statistics and analysed using generalised linear model (GLM) methods.

SO3: Acute pain score using VAS will be summarised using basic descriptive statistics and analysed using GLM methods.

SO4: Occurrence of non-delirium in-hospital complications within 30 days after surgery will be summarised by treatment group, but no relative effect will be calculated.

SO5: Length of hospital stay will be summarised using median and IQR and analysed using GLM methods.

9. Planned subgroup analyses

Interpretation of subgroup analysis will be treated with caution (output will be treated as exploratory rather than definitive[8]). Analysis will be limited to the primary outcome, which is the incidence of postoperative delirium during 7 postoperative days, and the following subgroups

- Age, as defined by 65-80, >80
- Preoperative dementia, those with vs those without
- Preoperative delirium, those with vs those without.

The effects of these subgroups will be examined by adding the subgroup by treatment group interaction parameters to the log-binomial model. Wald tests will determine statistical significance (p-values) of these interaction parameters. Differences between the treatment groups within subgroups will only be examined if the interaction parameter is shown to statistically important (p-value <0.05).

10. Definitions and Derived Variables

Abbreviations & Definitions	
Abbreviation/acronym	**Meaning**
BCTU	Birmingham Clinical Trials Unit
BP	Blood Pressure
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data Monitoring
ITT	Intention to Treat
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TSC	Trial Steering
POD	Postoperative Delirium
GA	General Anesthesia
RA	Regional Anesthesia
GLM	Generalised Linear Model
Term	**Definition**
International Standard Randomized Controlled Trial	A Clinical Trial Registry
Protocol	Document s details the rationale, objectives, design, methodology, and statistical considerations of the study
Randomisation	The process of assigning trial subjects to Intervention or control groups using an element of chance to determine the assignments in order to reduce bias.
Statistical Analysis Plan	Pre-specified statistical methodology documented for the trial, either at the protocol or in a separate document.

11. Software Details

Statistical analysis would be undertaken in the following statistical software packages: R.

References

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