The PROVOLON trial protocol revising and statistical analysis plan

Official Title of the trial: Effects of Open Lung Approach on Intraoperative Respiratory Function and Postoperative Recovery of Patients With Laparoscopic Colorectal Resection

Brief Title: The PROtective Ventilation using Open Lung approach Or Not trial (PROVOLON)

ClinicalTrials.gov ID: NCT03160144

Unique Protocol ID: 2017ZSLYEC-002

Document Date: September 11, 2017

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The Statistical Analysis Plan was developed prior to locking the trial database and starting analyses. The trial protocol is registered with ClinicalTrials.gov (NCT03160144), and was approved by the Institutional Review Boards (IRB). No amendment was performed to the statistical analysis plan since the last IRB approval of the study protocol.

Study framework and protocol revising

The design of the study is aimed at demonstrating superiority of protective mechanical ventilation (PV) with "open lung strategy (OLS)" including the use of positive end-expiratory pressure (PEEP) and recruitment maneuvers (RM), over PV without OLS in terms of 7-day postoperative complications and other outcomes.

This trial will be carried out in two stages. Completely-randomized design was used in the first stage, and randomized block design in the following stages. The interim analysis was performed when 100 patients had successfully been included and followed-up. After the interim analysis, the researchers found that the postoperative blood gas analysis was less operable (mainly due to the patient's refusal of painful operation), and the loss rate of chest X-ray was higher (the patients were reluctant to get out of bed). Considering patients interests is the highest ethical principle, in the follow-up study, we gave up the plan of taking the initiative to conduct blood gas analysis and recommended ward execution when necessary. We also adopted a strongly suggested but not mandatory plan for chest X-ray examination in the third day after surgery. Due to the above-mentioned changes of the study protocol, we have also made some modifications to the primary outcome events and their definitions. These modifications were discussed and agreed by the research group and approved by the data monitoring and safety group (DMSG) and IRB. The specific modifications are as follows: Major pulmonary complications were defined as suspected pneumonia, acute respiratory failure and sustained hypoxia.

Related events definition

1. Suspected pneumonia: patient receives antibiotics and meets at least one of the following criteria: (i) the presence of new and/or progressive pulmonary infiltrates on chest X-ray plus two or more of the following criteria: fever ≥ 38.5°C, leukocytosis ≥ 12000 WBC/mm^3 or neutrophil > 80%, purulent sputum and/or new onset or worsening cough or dyspnea, or (ii) without chest X-ray and in the absence of other infectious focus (i.e. urinary or biliary tract infection, intestinal obstruction, intraabdominal abscess or anastomotic leakage et al), and presence of three of the following criteria: fever ≥ 38.5°C, leukocytosis ≥ 12000 WBC/mm^3 or neutrophil > 80%, purulent sputum and/or new onset or worsening cough or dyspnea.

2. Postoperative acute respiratory failure: PaO2 < 60 mmHg or SpO2 < 90% lasting more than one minute on room air.

3. Sustained hypoxia: $SpO_2 \leq 92\%$ was observed more than three days consecutively

Sample size calculation

The required sample size was calculated from previous studies on the incidence of postoperative complications. A two group chi-square test with a 0.05 two-sided significance level would have 80% power to detect the difference (in primary outcome) between PV without OLS (25%) and PV with OLS (12.5%) when the sample size in each group is 126. In consideration of a 10% loss rate, 280 cases to be included in this study.

An interim analysis was performed for this trial in September, 2017. Results showed that the

intervention had a trend for improving postoperative complications and $p > 0.018$, as well as significant group-difference in adverse events was not observed ($p > 0.025$). The data monitoring and safety group (DMSG) recommended to continue the trial in 280 patients.

Timing of final analysis

All outcomes will be analyzed simultaneously after we have completed the 30-day follow-up of all patients and the database has been locked.

Statistical principles

Confidence intervals and P values

We will present 95% confidence intervals for effect estimates on all primary and secondary outcomes. All hypothesis tests will be two-sided with α of 5%.

Adherence and protocol deviations

We will report the numbers and percentages of non-adherence to randomly allocated treatment. Protocol deviations will be assessed and registered by the coordinators. Major deviations or violations are defined as wrong inclusion (misjudgment of inclusion or exclusion criteria) or inadequate resuscitation procedures during the study period.

Analysis populations

All outcome analyses will be conducted according to the modified intention-to-treat principle.

Intention-to-treat: All randomised patients. This population will be used in demographic data and baseline data analysis, but not in outcome analysis in the PROVOLON trial.

Modified intention-to-treat: All randomised patients except patients:

- for whom surgery had to conversion to laparotomy in half an hour after surgery start.
- for whom there was a severe surgical complications (i.e. bleeding, reoperation, et al) intraoperatively or within 24 hours after surgery.

This population will be used in outcome analysis.

Analysis

Primary outcome analysis

Primary outcome were defined as occurrence rate of major pulmonary and extrapulmonary complications.

Major pulmonary complications were defined as suspected pneumonia, acute respiratory failure and sustained hypoxia. Major extrapulmonary complications were defined as sepsis, severe sepsis, septic shock or death. Results will be reported as counts (%), relative risk with 95% confidence intervals (CI) and P-values. Unadjusted Chi-square test will be used for the primary outcome. Kaplan Meier curves will also be presented.

Secondary outcomes analysis

Continuous variables (i.e. PaO_2, PaO_2/FIO_2, Q_s/Q_T, RI, V_D/V_T, C_{dyn}, C_{sta}, driving pressure, plasma levels of sRAGE, postoperative hospital stay, et al) were expressed as means ± SD or as medians (interquartile range), which will be compared via independent t-tests or Mann–Whitney U tests, respectively.

Categorical variables (i.e. postoperative data including suspected pneumonia, acute respiratory failure and sustained hypoxia, sepsis, SIRS, death, AMI, intraabdominal abscess or anastomotic leakage, admission to intensive-care unit or intraoperative data including impaired oxygenation, rescue therapy for desaturation, potentially harmful hypotension, vasoactive drugs needed, et al) will be

presented as counts (%), and compared using the chi-squared test or Fisher's exact tests.

Harms

The primary and secondary outcomes are intended to reflect potential harms resulting from the cPV versus sPV for managing intraoperative respiratory function and postoperative complications.

Missing data

we will use raw data without imputation to analysis.

Statistical software

Analyses will be performed using the SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL, USA).

Conclusion

In accordance with best trial practices, statistical analysis plan and data management plan are herein reported before the database is locked, and previously to the beginning of the analyses.