African Surgical Outcomes Study in Paediatric patients (ASOS-Paeds)

An African, international multi-centre fourteen-day evaluation of patient care and clinical outcomes for paediatric patients undergoing surgery

Statistical analysis plan version 1
1 February 2023

Registration ClinicalTrials.gov - NCT05061407

Protocol Version 2.0

Alexandra Torborg

Chief investigator

Bruce Biccard

Steering committee

1. Alexandra Torborg MBChB FCA(SA), Discipline of Anaesthesiology and Critical Care Medicine, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

2. Bruce Biccard MBChB FCA(SA) FFARCS(I) MMedSci PhD, Professor and Second Chair, Department of Anaesthesia and Perioperative Medicine, Groote Schuur Hospital and University of Cape Town, South Africa

3. Rupert Pearse MD(Res), Professor of Intensive Care Medicine, Queen Mary University of London, Royal London Hospital, London, E1 1BB, United Kingdom

4. Priyanka Naidu MBChB, Department of Research, Education, and Innovation, Operation Smile, Virginia Beach, Virginia, USA, Centre for Global Surgery, Department of Global Health, Stellenbosch University, Tygerberg, South Africa.

5. Hyla Kluyts DMed (Anaest), Department of Anaesthesiology, Sefako Makgatho Health Sciences University, South Africa

6. Mary T. Nabukenya MMED, FCA(ECSA), Lecturer, Makerere University College of Health Sciences, Paediatric anaesthesiologist, Mulago National Referral Hospital, Kampala, Uganda

7. Adesoji O Ademuyiwa, FACS, Professor of Surgery (Paediatric and Surgical Epidemiology), Department of Surgery, College of Medicine, University of Lagos and Lagos University Teaching Hospital, Lagos, Nigeria

Principal investigator contact details

Dr Alexandra Torborg

Perioperative Research Group,

Department of Anaesthetics

Nelson R Mandela School of Medicine

Private Bag 7, Congella, 4013

Kwazulu-Natal, South Africa

E-mail: alexandra@iafrica.com

Telephone: +27 (0)833850217

Facsimile: +27 (0) 31 260 4433

Contents

Introduction

Surgery is a cost-effective public health intervention. There are significant disparities in access to and the safety of surgical and anaesthesia services in low and middle-income countries (LMICs) compared to high-income countries (HICs).[1] There is a large burden of surgical disease in the paediatric surgical population with a large unmet need.[2][3] In Africa, children comprise a significant proportion of the population with approximately 50% of the population being ≤19 years old.[4]

Postoperative complications are an important determinant of surgical morbidity and mortality. Limited data from Africa suggests the risk factors for, incidence and outcomes associated with paediatric surgical complications differ from HICs. In the prospective, observational South African Paediatric Surgical Outcomes Study (SAPSOS), the patients in this middle-income country (MIC),[5] had double the incidence of complications[6-8], and the types of complications differed from HICs, with a predominance of infective complications. Furthermore, the risk factors for complications (ASA physical status, urgency of surgery, severity of surgery and infective indication for surgery) were different from HICs, where risk factors include gestational age, ASA physical status >3, a history of cardiovascular disease, and cardiovascular, neurological, or orthopaedic surgical procedures.[9] Postoperative mortality was ten times higher in South Africa than in a prospective study in HICs.[10] A prospective study of paediatric perioperative mortality in 24 Kenyan hospitals showed a 7 day postoperative mortality of 1.7%.[11], which is 17 times higher than that reported in HICs.

The African Surgical Outcomes Study (ASOS) has described surgical outcomes in adult patients in Africa.[12] Patients had a lower risk profile and fewer complications compared to those in HICs. However, the postoperative mortality was twice that of the global average.

There is a need to determine the burden of the complications in paediatric surgical patients in Africa, and the risk factors for and the type of complications experienced. If we do this, we will be able to target appropriate interventions to improve surgical outcomes for children in Africa. We have the capacity to do this important work, through the African Perioperative Research Group (APORG) group.

Statistical Analysis Plan

Recruitment description
Site and patient recruitment and description will be presented as follows:
- Strobe flow diagram including i) countries (excluded and included), ii) number of eligible patients, iii) patients included and excluded,

- The patient and surgical characteristics of the cohort will be presented in a Table, and

- The number of participating hospitals and patients at each level will be reported

Categorical variables will be described as proportions and will be compared using chi-square tests. Continuous variables will be described as mean and standard deviation if normally distributed or median and inter-quartile range (IQR) if not normally distributed. No comparisons between groups will be performed at a univariate level. Data completeness will be reported as the frequency of missing data.

Objectives

Primary objective
To determine the incidence of in-hospital postoperative complications up to 30 days post-surgery in paediatric surgical patients <18 years in Africa

Statistical analysis plan for primary objective
We will present the number and proportion for these data. Complications will be reported as total, and mild, moderate and severe complications. The absolute incidence of complications will also be reported for i) Infective, ii) Cardiovascular and iii) Other.

Secondary objectives
In paediatric surgical patients < 18 years in Africa:
1. To determine the in-hospital peri-operative mortality rate up to 30 days post-surgery,

2. To determine the incidence of intraoperative severe critical incidents,

3. To determine the association between pre-operative, intra-operative and facility factors with postoperative complications and death.

Statistical analysis plan for secondary objectives

1. To determine the in-hospital peri-operative mortality rate up to 30 days post-surgery

We will present the number and proportion for these data for i) mortality on the day of surgery, and ii) mortality in hospital within 30 days of surgery.

2. To determine the incidence of intraoperative severe critical incidents,

We will present the number and proportion for these data, including individual severe critical incidents, and the categories of respiratory, cardiovascular, metabolic, drug error and death. ***(Severe critical incidents will be presented in a secondary paper)***

3. To determine the association between pre-operative, intra-operative and facility factors with postoperative complications and death.

The following risk factors will be entered into the model: i) Patient factors: i.e. age, gender, ASA, comorbidities, and ii) Surgical risk factors: i.e. urgency, severity, surgical discipline, surgery out of hours, surgery duration.

The model outcomes will be: i) all complications, and ii) death.

The models will only include patients with complete outcome data (i.e. patients who are still in hospital receiving therapy, and have not reached the outcome definition of death, discharge, or in-hospital at 30 days will be excluded). Generalized linear mixed models using a logit link will be used to identify independent risk factors for the binary outcome of mortality. We will use a three-level generalized mixed model, with patients being at the first level, hospital at the second and country at the third level, to account for the expected correlation in outcomes within hospitals and countries. We will exclude patients with missing values for potential risk predictors, and only use a complete case analysis if there are <5% of the dataset with incomplete potential clinical risk predictors. All risk factors will be entered into the model, unless the number of reported deaths is insufficient to provide 10 events (deaths) per variable. Should the events per variable be <10, then variables with a univariate association of $p<0.05$, and variables with biological plausibility and a low rate of missing data will be used.

Collinearity will be assessed using the variance inflation factor. If collinearity is detected, then variables will either be excluded or combined. The model fit will be evaluated.

Results of the logistic regression will be reported as adjusted odds ratios (OR) with 95% confidence intervals (CI). The models will be assessed through the use of sensitivity analyses to explore possible interacting factors and examine any effect on the results.

Univariate and multivariate statistical analyses will be performed using the Statistical Package for the Social Sciences (SPSS) version 28.0.1.1 (SPSS Inc., Chicago, IL, USA).

Sensitivity analyses will be conducted for the primary outcome, which will include:
1. Elective surgical cohort only,

2. Emergency surgical cohort only and

3. A cohort excluding patients with a current or recently diagnosed Covid-19 infection (defined as confirmed Covid-19 infection from 7 weeks preoperatively to 30 days postoperatively).

Results will be reported as adjusted odds ratios (OR) with 95% confidence intervals.