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

Substudy: Facility factors associated with mortality following paediatric surgery in Africa.

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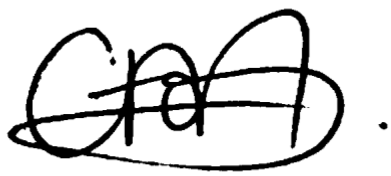

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Introduction

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.

The ASOS-Paeds study confirmed the burden of complications following surgery in Africa, and identified the high-mortality following surgery, and those patient and surgical risk factors associated with mortality.[13] However, the reporting by the clinicians that the operating rooms were not always safe for paediatric surgery, suggests that there are facility factors associated with mortality following paediatric surgery in Africa.[13] Previously it has been shown that approximately 40% of mortality in adult cancer surgical patients can be attributed to the facility and country factors.[14]

The aim of this study is to determine the proportional contribution of facility factors to mortality following paediatric surgery in Africa.

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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) facilities (included and excluded), iii) number of eligible patients, iv) patients included and excluded,
- The patient and surgical characteristics of the cohort will be presented in a Table (Table 1), and
- The number of participating hospitals (facilities) and patients at each level will be reported (Supplementary Table), and
- The characteristics of the facilities, including the facility factors (Table 2).

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 proportion of in-hospital deaths attributable to facility factors 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 proportions for these facility data. The statistical analysis will follow three stages:

1. Backward entry of facility factors in a generalized linear mixed model (GLMM) for in-hospital mortality which includes the patient and surgical risk factors independently associated with mortality.[13]

The facility factors identified for entry into the model include: i) Hospital level of care (3 categories), ii) Volume of surgery (<x number of cases per month, determined by the optimal cut point) (generate ROC for cut point), iii) whether the hospital administration capture variables that can be used to determine perioperative mortality, iv) presence of incubators or warning devices, v) whether the operating room was considered safe for surgery and anaesthesia for <1 year old, vi) whether the operating room considered safe for surgery and anaesthesia for patients between 1 and 6 years old, vii) reliable oxygen supply always available, viii) reliable electricity supply always available, viii) atropine always available, ix) adrenaline always available, x) the ability to do blood transfusions, xi) the presence of critical care beds for invasive ventilation, xii) the use of the surgical safety checklist, and xiii) the presence of a dedicated paediatric emergency airway trolley in the operating complex.
The probability of the outcome of mortality predicted for each patient will be calculated, and the aggregate predicted outcome probability (by tertile) presented. We also present the distribution of outcomes across hospital level i.e. district, regional, tertiary (Table 3).

2. The attributable fraction for mortality associated with facility factors will be calculated from the facility factors included in the final model.

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. Facility factors will be backwards entered into the model. The patient and surgical factors from the main analysis will be entered into the model to account for confounding.[13] We will ensure that we have at least 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. The facility factors independently associated with in-hospital mortality will be shown in Table 4.

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 using sensitivity analyses to explore possible interacting factors and examine any effect on the results.

3. Directed acyclic graph (DAG) and mediation analysis of mortality with patient, surgical and facility factors as mediators.

- Exposure: Country income groups: i) low, ii) lower-middle, and iii) upper-middle or high
- Outcome: 30-day in hospital mortality
- Mediators
    - Independent patient factors as in ASOS-Paeds publication: age, ASA category, cardiac disease, neurological disease, current respiratory tract infection, other comorbidities
    - Independent surgical factors as in ASOS-Paeds publication: urgency of surgery, burns surgery, duration of surgery
    - Facility factors: none of the proposed factors are considered to have a causal relationship with the surgical factors.

Bootstrapped 95% CIs through percentile bootstrapping will account for uncertainty. We assume no causal relationships of patient and surgical factors with facility factors.

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) and R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing (2024) using Studio: Integrated Development Environment for R. Boston, MA: RStudio, Inc. (2024).

Sensitivity analysis will be conducted for the primary outcome

The sensitivity analyses will include:

1. Excluding countries which provided data >10% of the cohort

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

References

1. Bainbridge D, Martin J, Arango M, et al. Perioperative and anaesthetic-related mortality in developed and developing countries: a systematic review and meta-analysis. *Lancet* 2012;380(9847):1075-81. doi: 10.1016/s0140-6736(12)60990-8 [published Online First: 2012/09/25]
2. Bickler SW, Rode H. Surgical services for children in developing countries. *Bull World Health Organ* 2002;80(10):829-35. [published Online First: 2002/12/10]
3. Butler EK, Tran TM, Nagarajan N, et al. Epidemiology of pediatric surgical needs in low-income countries. *PLoS One* 2017;12(3):e0170968. doi: 10.1371/journal.pone.0170968 [published Online First: 2017/03/04]
4. 2014 World Population Data Sheet, 2014.
5. Torborg A, Cronje L, Thomas J, et al. South African Paediatric Surgical Outcomes Study: a 14-day prospective, observational cohort study of paediatric surgical patients. *Br J Anaesth* 2019;122(2):224-32. doi: 10.1016/j.bja.2018.11.015 [published Online First: 2019/01/29]
6. GlobalSurg C. Determinants of morbidity and mortality following emergency abdominal surgery in children in low-income and middle-income countries. *BMJ Glob Health* 2016;1(4):e000091. doi: 10.1136/bmjgh-2016-000091 [published Online First: 2017/06/08]
7. Weinberg AC, Huang L, Jiang H, et al. Perioperative risk factors for major complications in pediatric surgery: a study in surgical risk assessment for children. *J Am Coll Surg* 2011;212(5):768-78. doi: 10.1016/j.jamcollsurg.2011.02.006 [published Online First: 2011/03/26]
8. Saito JM, Chen LE, Hall BL, et al. Risk-adjusted hospital outcomes for children's surgery. *Pediatrics* 2013;132(3):e677-88. doi: 10.1542/peds.2013-0867 [published Online First: 2013/08/07]
9. Wood G, Barayan G, Sanchez DC, et al. Validation of the pediatric surgical risk assessment scoring system. *J Pediatr Surg* 2013;48(10):2017-21. doi: 10.1016/j.jpedsurg.2013.04.017 [published Online First: 2013/10/08]
10. Habre W, Disma N, Virag K, et al. Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. *Lancet Respir Med* 2017;5(5):412-25. doi: 10.1016/S2213-2600(17)30116-9 [published Online First: 2017/04/02]
11. Newton MW, Hurt SE, McEvoy MD, et al. Pediatric Perioperative Mortality in Kenya: A Prospective Cohort Study from 24 Hospitals. *Anesthesiology* 2019 doi: 10.1097/ALN.0000000000003070 [published Online First: 2019/12/07]
12. Biccard BM, Madiba TE, Kluyts HL, et al. Perioperative patient outcomes in the African Surgical Outcomes Study: a 7-day prospective observational cohort study. *Lancet* 2018;391(10130):1589-98. doi: 10.1016/S0140-6736(18)30001-1 [published Online First: 2018/01/08]
13. Torborg A, Meyer H, El Fiky M, et al. Outcomes after surgery for children in Africa (ASOS-Paeds): a 14-day prospective observational cohort study. *The Lancet* doi: 10.1016/S0140-6736(24)00103-X
14. Global variation in postoperative mortality and complications after cancer surgery: a multicentre, prospective cohort study in 82 countries. *Lancet* 2021;397(10272):387-97. doi: 10.1016/s0140-6736(21)00001-5 [published Online First: 2021/01/25]