Latin **A**merican **S**urgical **O**utcomes **S**tudy in **P**ediatric patients

LASOS-Peds

Clinical study protocol

Version 1.0

April 2023

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São Paulo

2023

LASOS-Peds
Latin American
Surgical Outcomes
Study in Pediatrics

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Summary

Short Title	LASOS-Peds
Methods	Prospective, international, multicenter observational study.
Centers	Hospitals performing pediatric surgery in participating Latin American countries.
Objectives	To assess the incidence of hospital postoperative complications in pediatric surgical patients < 18-years-old in Latin America.
Participants	10,000.
Inclusion criteria	All consecutive pediatric patients under the age of 18 years who were admitted to participating hospitals undergoing elective and nonelective surgery.
Exclusion criteria	Obstetrics.
Primary Outcome	The primary outcome is in-hospital postoperative complications up to 30 days after surgery.
Follow-up	Until hospital discharge, or a maximum of 30 days.

Background

Surgery is a cost-effective public health intervention. However, there are significant disparities in access to and in the safety of surgical and anesthesia services in low- and middle-income countries compared to high-income countries. (1) Additionally, there is a significant burden of surgical disease in the pediatric surgical population with a significant unmet need. (2,3) In Africa, children represent a significant proportion of the population, with approximately 50% of the population aged <19 years; moreover, this proportion is very similar in Latin America. (4)

Postoperative complications are an important determinant of surgical morbidity and mortality. Limited data from Africa and Latin America suggest that risk factors, incidence, and outcomes associated with pediatric surgical complications differ in high-income countries. In the South African Pediatric Surgical Outcomes Study (SAPSOS), patients in this middle-income country (5) had twice the incidence of complications (6-8), and the types of complications differed from those in high-income countries, with a predominance of infectious complications. Furthermore, risk factors for complications (including ASA physical status, urgent surgery, surgery severity, and infectious indication for surgery) were different from those in high-income countries, wherein the risk factors include post-conceptual age, ASA physical status > 3, history of cardiovascular disease, and cardiovascular, neurological, or orthopedic surgical procedures. (9) Postoperative mortality was observed to be ten times higher in

South Africa than in a prospective study in high-income countries. (10) Furthermore, a prospective study of pediatric perioperative mortality in 24 Kenyan hospitals demonstrated a 7-day postoperative mortality of 1.7% (11), which is 17 times higher than that reported in high-income countries.

The African Surgical Outcomes Study (ASOS) described surgical outcomes in African adult patients. (12) Specifically, patients had a lower risk profile and fewer complications than those in high-income countries. However, postoperative mortality was twice the global average. A similar study is being performed in Latin America (LASOS), which also includes adults.

It is necessary to determine the importance of complications in pediatric surgical patients in Latin America, as well as the risk factors and types of complications that are experienced by these patients, due to the fact that data on this population are scarce. Consequently, we will be able to target appropriate interventions and funding to improve surgical outcomes for children in Latin America.

Study objectives

Primary objective

To determine the incidence of in-hospital postoperative complications up to 30 days after surgery in Latin American pediatric surgical patients (under 18-years-old).

Secondary objectives

In pediatric surgical patients under 18 years of age in Latin America, we aim to:

1. determine the perioperative in-hospital mortality rate up to 30 days after surgery;
2. determine the incidence of severe intraoperative adverse events;
3. determine the association between preoperative, intraoperative, and infrastructural factors and postoperative complications and death.

Methods

Study design

14-day Latin American international multicenter prospective cohort study of pediatric patients (<18 years) undergoing surgery.

Inclusion criteria

All of the consecutive patients under 18-years-old who were admitted to participating hospitals during the study period and who underwent elective and nonelective surgeries will be included in the study. This analysis will include outpatient surgeries and surgical procedures outside of operating rooms requiring local or general anesthesia. Recruitment will occur for fourteen days, starting on the date chosen by each participating hospital within the study cohort period (to be determined).

Exclusion criteria

1. patients undergoing radiological or other procedures that do not require general anesthesia or in which general anesthesia is performed but no procedure is performed (e.g., general anesthesia during MRI);
2. patients undergoing obstetric surgery.

Hospitals

Our goal is to recruit as many Latin American hospitals as possible. Each hospital will receive an individual report that compares its dataset with that of the overall national cohort.

Ethics in research and informed consent

Research ethics and regulatory approvals will be sought before the initiation of the study in each location by using national research legislation/guidelines for that country.

National leaders will ensure that the necessary ethical and regulatory approvals are obtained for participating hospitals in their country. Hospitals can only record data if there is ethical approval or an equivalent waiver.

This study is a large-scale clinical audit; therefore, it does not pose a significant risk to the study population. In most, if not all, countries, there will be no requirement for individual patient consent, as all of the data will be anonymized and are expected to be recorded as part of routine clinical practice.

A precedent has already been set from an international perspective. In the original EuSOS study, consent was provided in 27 of the 28 participating European countries. (13) In the ASOS study (12) and the ASOS-2 trial, consent was provided in most hospitals. In African pediatric perioperative studies, written informed consent was provided by six of eight ethics committees in the SAPSOS

(5) study. Additionally, in a study in Kenya, written informed consent was provided in all 24 participating hospitals. (11) The LASOS study also obtained a consent form waiver from the coordinating center (Hospital das Clínicas HCFMUSP).

Informational signage documents will be used at participating sites to ensure that all of the patients and parents/guardians know that the hospital is participating in the study. These handover documents will be placed in critical areas of the participating hospitals, with explanations of the dates and nature of the study.

Recruitment and screening

We expect that all consecutive pediatric patients under 18 years undergoing elective and nonelective surgeries will be included in the study. Each hospital must record and submit a triage record of all of the eligible patients. Publicity through the appropriate hospital notices and signage will inform patients, their parents/guardians, and the public that the hospital is participating in the study.

Data collection and grouping

Each hospital will individually collect and record data on an electronic or paper case recording form (CRF) for each recruited patient. Paper CRFs will be stored in a locked office at each hospital, as they will include patient-identifiable data to allow for the tracking of clinical outcomes.

Data will be pseudoanonymized by generating a unique numeric code and transcribed by local investigators into a secure, password-protected electronic CRF on the REDCap platform. Each patient will be solely identified on the electronic CRF by their numerical code; thus, the study coordinating team can only trace the data back to an individual patient with contact with the local team. A participant (patient) list will be used at each hospital to match the identification codes in the database to individual patients to record clinical results and to provide any missing data points. Access to the data entry system will be protected by the username and password provided during the registration process to individual local investigators. All of the electronic data transfers between participating hospitals and the coordinating center will be encrypted by using a secure protocol (HTTPS/SSL 3.0 or higher).

When individual hospitals are unable to access the registration form over the internet, pseudoanonymous coded data can also be faxed, registered mailed, emailed, or WhatsApp messaged to the coordinating center (if necessary).

Each hospital will maintain a secure trial file, including a protocol, local investigator delegation record, ethics approval documentation, participant list, and other documentation (such as trial definitions).

A printout of the final summary of the included patients with essential variables should be produced for each hospital, along with the submission of final data for double-checking for completeness and accuracy.

Dataset

A realistic dataset will be critical to the success of the investigation, and this requirement was confirmed in the EuSOS (13), SASOS (14), and SAPSOS (5) studies, wherein almost complete data were available on the patients. Based on the SAPSOS and ASOS-Paeds study, we plan to adopt this dataset with minor changes to remove data that are deemed to be redundant to develop a simple, lean, and pragmatic dataset. We believe this simple dataset will encourage hospitals to participate.

Hospital-specific data will be collected once, including hospital level of care (primary, secondary, and tertiary), number of operating rooms, number of specialists, number and level of intensive care beds, equipment suitable for pediatric surgery and anesthesia, availability of drugs and blood products, details of hospital reimbursement status, and holidays or other local factors that affect patient flow during the study period.

Case registration forms

A CRF LASOS-Peds will be completed for each eligible patient who undergoes surgery during the cohort period. Patients will be followed up until hospital discharge. This will be censored in thirty days; specifically, patients will be followed up until discharge or for thirty days after surgery if they are still in the hospital.

Sample size calculation

We plan to recruit as many hospitals from each participating country as possible and ask them to include all eligible patients in the study. We do not have a specific sample size, and statistical models will be adapted to the event rate provided by the recruited sample to avoid inappropriate use of any logistic regression models.

Statistical analysis

The data to be collected are all collected as part of routine clinical care. Categorical variables will be described as proportions and compared by using chi-square tests. Continuous variables will be described as the mean and standard deviation if normally distributed or as the median and interquartile range if not normally distributed. The univariate analysis will test factors associated with postoperative complications, intensive care admission, and in-hospital death.

Hierarchical multilevel logistic regression models will be constructed to identify factors that are independently associated with these outcomes and to adjust for differences in confounding factors. Factors will be entered into the models based on their univariate relationship with the outcome ($p<0.05$), biological plausibility, and low rate of missing data. Logistic regression results will be reported as adjusted odds ratios (ORs) with 95% confidence intervals. Moreover, models will be evaluated by using sensitivity analyses to explore

possible interacting factors and to examine any effect on the results. A statistical analysis plan will be written before the analysis.

Primary outcome

Postoperative complications in the hospital up to 30 days after surgery.

Secondary outcomes

1. Mortality on the day of surgery;
2. Hospital mortality up to 30 days after surgery;
3. Risk factors associated with in-hospital complications;
4. Severe intraoperative critical adverse events;
5. Level of qualification of anesthesia and surgery providers, as well as the number of specialists per pediatric population;
6. Admission to intensive care.

Study organization and management

Study steering committee

The Steering Committee will be chaired by the leading researcher. The study management team will be appointed by the Steering Committee and led by the principal investigator. This team's duties will include the following:

- administration of all project tasks;
- communication between project partners (including funders, Steering Committee members, and national and local coordinators);
- data collection and management;
- preparation of reports to project sites;
- individual study.

The Steering Committee is responsible for the scientific conduct and consistency of the project. The Steering Committee will ensure communication between the funder(s), the trial management team, and coordinators, as needed.

National coordinators

The Steering Committee will appoint national coordinators to lead the project in each country and:

- identify local coordinators at participating hospitals;
- assist in translating study paperwork, as needed;

- ensure the distribution of research manuals and other research materials;
- ensure necessary regulatory and ethical approvals are in place before recruitment;
- ensure good communication with participating sites in your country.

Local coordinators

Local coordinators at individual institutions will have the following responsibilities:

- provide leadership for study at your institution;
- ensure that all relevant regulatory and ethical approvals are in place for your institution;
- ensure proper training of all relevant personnel before data collection;
- oversee daily data collection and site recruitment, as well as follow-up on management;
- act as a guarantor of the integrity and quality of the collected data;
- ensure the timely completion of electronic CRFs;
- communicate with the national coordinator.

Investigator training

Training will be performed by using instructional videos posted on the study website. Each site must complete an online questionnaire as part of the baseline before starting data collection.

Data management and ownership

On behalf of the Steering Committee, the Academic Research Organization of Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo will be a data custodian. The Steering Committee will retain the right to use all of the pooled data for scientific and other purposes. The LASOS-Peds study group members will have the right to access the pooled data for research purposes, provided that the research proposal has been reviewed and deemed appropriate by the Steering Committee. The primary consideration for such decisions will be the quality and validity of any proposed analysis. Only summarized data will be presented publicly, and all of the institutions will be anonymized (except in the individualized report provided to each institution at the end of the study). Individual patient data supplied by participating centers remain the property of the respective institutions.

Publication plan

Data will be promptly edited and released. The Steering Committee will appoint a Writing Committee to write this investigation's scientific report(s). The group will be known as 'The LASOS-Peds Investigators'. It is anticipated that several secondary analyses will be performed. LASOS-Peds investigators will be given priority to conduct such analyses and encouraged to do so. Participation and authorship opportunities will be based on contributions to the primary study. Upon request, hospitals will receive an individual report that allows for the comparison of the summary data from their particular hospital with that of their national cohort. In conjunction with the principles of data preservation and sharing, the Steering Committee will consider all reasonable requests to make the dataset available in whole or in part for secondary analysis and scientific publication upon publication of the general dataset. The Steering Committee will consider scientific validity and the possible effect on the anonymity of participating hospitals before granting such requests. Where appropriate, a prior written agreement will set out the terms of such collaborations. The Steering Committee will consider proposals for secondary reviews based on the scientific quality of the proposal. Furthermore, the Steering Committee must approve the final version of all of the manuscripts before submission, whether they relate to part or all of the LASOS-Peds dataset.

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