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*H*igh-flow oxygen for children's *a*irway surgery: rando*m*i*s*ed controll*e*d *t*rial protocol (HAMSTER)

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ABSTRACT

Introduction Hypoxaemia during anaesthesia for tubeless upper airway surgery in children with abnormal airways is common due to the complexity of balancing adequate depth of anaesthesia with maintenance of spontaneous breathing and providing an uninterrupted field of view of the upper airway for the surgeon. High-flow nasal oxygenation (HIGH-FLOW) can prolong safe apnoea time and be used in children with abnormal airways but to date has not been compared with the alternative technique of low-flow nasal oxygenation (LOW-FLOW). The aim is to investigate if use of HIGH-FLOW can reduce the number of hypoxaemic events requiring rescue oxygenation compared with LOW-FLOW.

Methods and analysis *H*igh-flow oxygen for children's *a*irway surgery: rando*m*i*s*ed controll*e*d *t*rial (HAMSTER) is a multicentre, unmasked, randomised controlled, parallel group, superiority trial comparing two oxygenation techniques during anaesthesia. Children (n=530) aged >37 weeks to 16 years presenting for elective tubeless upper airway surgery who fulfil inclusion but not exclusion criteria will be randomised prior to surgery to HIGH-FLOW or LOW-FLOW post induction of anaesthesia. Maintenance of anaesthesia with HIGH-FLOW requires Total IntraVenous Anaesthesia (TIVA) and with LOW-FLOW, either inhalational or TIVA at discretion of anaesthetist. The primary outcome is the incidence of hypoxaemic events requiring interruption of procedure for rescue oxygenation by positive pressure ventilation and the secondary outcome includes total hypoxaemia time, adverse cardiorespiratory events and unexpected paediatric intensive care admission admission. Hypoxaemia is defined as SpO_2 <90%. Analysis will be conducted on an intention-to-treat basis.

Ethics and dissemination Ethical approval has been obtained by Children's Health Queensland Human Research Ethics Committee (HREC/18/QRCH/130). The trial commenced recruitment in 2018. The primary manuscript will be submitted for publication in a peer-reviewed journal.

Trial registration number The HAMSTER is registered with the Australia and New Zealand Clinical TrialsRegistry: ACTRN12618000949280.

Strengths and limitations of this study

- The primary outcome is pragmatically chosen to represent clinical relevance of the hypoxaemia event.
- The risk of selection and allocation bias will be reduced through the use of computer-generated randomisation and allocation concealment.
- High-flow and low-flow nasal oxygenation are not amenable to blinding of patients, clinical or research staff.
- The study only compares oxygenation techniques but the anaesthesia techniques may independently contribute to differences in outcomes.

INTRODUCTION

Tubeless upper airway surgery is a common procedure performed in children with airway abnormalities for a variety of diagnostic and therapeutic indications. These 'shared airway' cases pose particular challenges to both anaesthetist and surgeon. For the anaesthetist, the balance of simultaneous maintenance of airway patency, spontaneous respiratory effort and maintenance of adequate oxygenation and ventilation, along with sufficient depth of anaesthesia, is complex. These conditions must be achieved while allowing for an unobstructed operative field view and minimal surgical interruption. Spontaneous ventilation is frequently required to allow dynamic airway assessment and it is often impractical to place an endotracheal tube.[1]

Inadvertent hypoxaemia during airway surgery has implications for surgical efficiency and efficacy, and for patient safety. We conducted a clinical audit of 87 consecutive cases within our department of children undergoing dynamic airway assessment and we found that 34% of children had at least one hypoxaemic event and 23% of procedures were interrupted for rescue oxygenation. The onset of desaturation in apnoeic

infants and children is much faster than in adults and is known to be age dependent.[2 3] In small infants, apnoea can occur frequently and therefore balancing adequate depth of anaesthesia with spontaneous ventilation is often very difficult in this age group.

There are two main options for delivering fresh gas for oxygenation during tubeless upper airway surgery. The first is delivery of oxygen via a nasopharyngeal tube or insufflation catheter attached to the anaesthesia breathing circuit, delivering oxygen typically at flow rates up to 6 L/min as a low-flow nasal oxygen insufflation (LOW-FLOW) system. The second method is described as a high-flow nasal oxygen insufflation (HIGH-FLOW) system with delivery of heated (37°C) and humidified (100%) fresh gas at weight-related flow rates matching peak inspiratory flow, thereby allowing a known inspired fraction of oxygen via nasal cannula. This is not attached to an anaesthetic circuit hence requiring Total IntraVenous Anaesthesia (TIVA) for maintenance of anaesthesia. Currently, the choice of techniques is dependent on the anaesthetist's preference.

HIGH-FLOW has several known clinical benefits in spontaneous breathing which include the washout of nasopharyngeal dead space, reduction of inspiratory resistance, improved respiratory mechanics and provision of a 'splinting effect' by a positive distending pressure.[4] The LOW-FLOW system, a more traditional technique for oxygenation during tubeless upper airway surgery, is limited by its inability to humidify or heat the inhaled gas. The gas flow rates delivered are substantially lower with subsequently no added positive expiratory pressure respiratory support.

In adult anaesthesia, techniques similar to HIGH-FLOW, called transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) have been successfully used to prolong apnoeic oxygenation time in patients with difficult airways and in spontaneously breathing adults undergoing elective laryngotracheal surgery.[5] We have previously shown in anaesthetised and paralysed children that THRIVE is an effective oxygen delivery technique preserving adequate oxygen saturation during apnoea.[2] We have also shown alternatively that HIGH-FLOW can be successfully used in spontaneously breathing children with abnormal airways undergoing tubeless airway surgery.[6]

Oxygen Reserve Index, a prediction of hypoxaemia

Although clinicians aim to provide stable and safe oxygenation during such cases, monitoring of the respiratory system and oxygenation are crucial to detect failures in these processes, and allow early intervention to minimise the risks of hypoxaemia. Traditional measures include direct physical observation of patient chest movement, palpation of chest and abdominal movements under a surgical drape, pulse oximetry and respiratory impedance monitoring. Pulse oximetry has substantially improved clinician's awareness of desaturation and hypoxaemic episodes, but in younger infants and children with little respiratory reserve, desaturation from a normal transcutaneous oxygen saturation (SpO_2) can happen extremely rapidly. Any additional warning of impeding desaturation may markedly reduce the incidence of dangerous desaturations in such procedures. The Oxygen Reserve Index (ORI, Masimo) is a metric derived from multiwavelength pulse oximetry that includes information about venous saturation. Increases in venous saturation that occur with high PaO_2 act as an oxygen reserve, and the ability of ORI to monitor a reduction in this reserve may alert clinicians to impending arterial desaturation 30 s to 1 min before the desaturation is detected by ordinary pulse oximetry.[7 8] The clinical application of this method and its capacity to predetermine pending hypoxaemia needs to be tested in a clinical trial. The combination of a preventive method (HIGH-FLOW) with a predictive tool (such as ORI) strengthen the clinical significance of our proposed application.

Knowledge gap

To date, the rigorous evaluation of any oxygenation method to reduce anaesthetic complications such as hypoxaemia and interruption of procedure for rescue oxygenation has not been undertaken. There is no evidence for which of the current practices, HIGH-FLOW or LOW-FLOW, is superior in reducing hypoxemic events. The aim of this study is to compare, in a multicentre randomised trial, the proportion of hypoxaemic events requiring rescue oxygenation between HIGH-FLOW and LOW-FLOW in infants and children undergoing elective tubeless upper airway surgery.

We hypothesise that the higher flow rates of heated and humidified 100% oxygen using HIGH-FLOW could confer advantages over low-flow techniques during anaesthesia of spontaneously breathing infants or children for elective tubeless upper airway surgery.

The primary objective of the study is to compare proportion of rescue oxygenation attempts to manage hypoxaemia during anaesthesia for upper airway surgery between HIGH-FLOW and LOW-FLOW.

The secondary objective of the study is to demonstrate if HIGH-FLOW reduces the severity of hypoxaemia, the incidence of adverse cardiorespiratory events and unexpected paediatric intensive care admission (PICU) admissions.

METHODS

Design and settings

The *h*igh-flow oxygen for children's *a*irway surgery: rando*m*i*s*ed controll*e*d *t*rial (HAMSTER) is multicentre randomised controlled trial (RCT) which will be conducted across tertiary/quaternary paediatric anaesthesia departments in Australia (Queensland Children's Hospital, Brisbane The Children's Hospital, Westmead, Women's and Children's Hospital, Adelaide, Royal Children's Hospital, Melbourne and Perth Children's Hospital, Perth).

Table 1 Inclusion and exclusion criteria for high-flow oxygen for children's airway surgery: randomised controlled trial

Inclusion criteria	Exclusion criteria
► 0 (>37 weeks gestational)—16 years of age (15 years+364 days) ► Elective tubeless upper airway surgery*	► Tracheostomy in situ ► Requirement for laser surgery ► Known choanal atresia ► HIGH-FLOW contraindication†

* Where a tubeless airway management technique is required for the procedure.
† Recent cranial and/or mid-face surgery/trauma,cerebrospinal fluid leak.
HIGH-FLOW, High-flow nasal oxygen insufflation.

Participants

Children will be identified and recruited within the participating hospitals by screening of consecutive elective ENT lists for tubeless upper airway surgery. Patients meeting all inclusion criteria and no exclusion criteria (table 1) are eligible for randomisation.

Interventions

HIGH-FLOW technique

HIGH-FLOW will be delivered via the Optiflow device at weight-specific flow rates[6] (table 2) delivering a FiO_2 of 1.0. Jaw thrust will be applied to ensure a patent airway until airway instrumentation begins. Anaesthesia will be maintained via a TIVA using a combination of Propofol±an opioid at the discretion of the attending anaesthetist. Anaesthetists may wish to omit opioids in certain circumstances and this will be at the discretion of the anaesthetist, for example, neonates. Anaesthesia infusions will be adjusted to maintain both adequate depth of anaesthesia and spontaneous ventilation during procedure.

LOW-FLOW technique (usual care)

Oxygen insufflation at a flow rate of up to 6 L/min via a nasopharyngeal tube or catheter (LOW-FLOW). Jaw thrust will be applied to ensure a patent airway until airway instrumentation begins, and after airway instrumentation is complete. Anaesthesia will be maintained at the discretion of the anaesthetist, via inhalational anaesthesia, intravenous agents or a combination of both. Anaesthetists may wish to omit opioids in certain circumstances and this will be at the discretion of the anaesthetist, for example, neonates.

Table 2 HIGH-FLOW flow rates during anaesthesia

Weight	HIGH-FLOW flow rates
0–12 kg	2 L/kg/min
13–15 kg	30 L/min
16–30 kg	35 L/min
31–50 kg	40 L/min
>50 kg	50 L/min

HIGH-FLOW, high-flow nasal oxygen insufflation.

Blinded oxygenation and ventilation monitoring

In addition to the standard anaesthesia monitoring that provides the anaesthetist with the relevant clinical information to anaesthetise the child, continuous monitoring of the transcutaneous CO_2 ($TcCO_2$) and the ORI will be performed. These measurements will be captured during the entire procedure but will remain blinded to the operator so as not to impact on the decision-making process during the procedure. The data will remain blinded for the primary outcome assessment until recruitment of the last subject.

Anaesthesia technique

All patients

Anaesthesia will be induced as per individual anaesthetic practice of the operator and then intravenous access attained. The epiglottis, vocal cords and trachea will be visualised by direct laryngoscopy and topicalised with at least 4 mg/kg of lignocaine via a mucosal atomiser device prior to airway instrumentation. All other medication not relevant to the study outcome will be administered at the discretion of the individual anaesthetist. Oxygen delivery technique as per randomisation allocation will be applied and the procedure commenced. For both interventions, the individual recovery process from the anaesthesia will be at the discretion of the attending anaesthetist.

Interventionists

All anaesthetists involved in study are competent in both oxygenation and anaesthesia techniques and comply with randomisation decision. Both proposed techniques are currently used for tubeless upper airway surgery.

Management of hypoxaemic events requiring rescue oxygenation

A rescue oxygenation attempt occurs when the patient desaturates below a clinically accepted safe level. This rescue attempt is usually discussed and coordinated between the anaesthetist and the surgeon. If a rescue attempt is required, this will be dictated by the anaesthetist dependent on the patient's circumstances, which reflects current standard practice. The study procedure does not provide strict guidance on handling of hypoxaemic events as the primary outcome only addresses a reduction of the proportion of hypoxaemic events requiring rescue oxygenation. As a general rule, if the saturation levels drop <90%, most anaesthetists will attempt to initiate a rescue oxygenation attempt but if the surgical procedure is finishing, lower saturation may be acceptable for a short period of time.

Concomitant investigations

For combined procedures such as tonsillectomy or bronchoscopy/imaging, this study will include the

Box 1 Primary and secondary outcomes of the high-flow oxygen for children's airway surgery: randomised controlled trial

Primary outcome

1. Successful anaesthesia without any rescue oxygenation attempt for a hypoxaemic event.

Hypoxaemia: normally, hypoxaemia for anaesthesia is defined as an oxygen saturation of ≤90%.[4–6] However, dependent of the patient's physiology, age and starting saturation levels prior to the procedure, the anaesthetist can accept transiently lower oxygen levels if required to allow an uninterrupted surgical procedure. For the purpose of this study, we will not define a specific threshold for acceptable oxygen saturations as these are defined case by case. Similarly, the surgical procedure can contribute to hypoxaemia and acceptance of this is again at the discretion of the anaesthetist and surgeon. The investigators' view is that a hypoxaemic event that requires rescue intervention irrespective of the cause is the true and important outcome measure for this study. Hypoxaemic events due to surgical interventions such as airway ballooning will not contribute to the primary outcome but will be analysed separately. *Rescue oxygenation*: the surgical procedure is interrupted and the anaesthetist attempts to improve oxygenation of the child using either bag mask ventilation, insertion of an endotracheal tube or laryngeal mask followed by positive pressure ventilation.

Secondary outcomes

2. Total length of time patient experiences hypoxaemia (seconds) during hypoxaemic event (area under the curve) during the entire procedure
3. Minor adverse events: occurrence of epistaxis, laryngospasm, bronchospasm, coughing at any time during procedure
4. Major adverse events: occurrence of hypotension requiring treatment, bradycardia requiring treatment, cardiac arrest with or without return of spontaneous circulation at any time during procedure
5. Requirement for unexpected paediatric intensive care admission (PICU)
6. Requirement for unanticipated postoperative mechanical ventilation or any other form of non-invasive ventilation including high-flow nasal oxygen
7. Length of PICU stay
8. Length of hospital stay
9. Neurodevelopment at 6-months post intervention

anaesthetic period of only the tubeless upper airway surgery procedure.

Outcome measures and definitions

The primary outcome is *successful anaesthesia* without any rescue oxygenation attempt for a hypoxaemic event during tubeless upper airway surgery. Full definitions of both primary and secondary outcomes are provided in box 1.

SAMPLE SIZE AND STATISTICAL ANALYSIS PLAN

Sample size

At Queensland Children's Hospital in 2016, approximately 230 children fulfilled the study inclusion criteria and an audit of all tubeless airway procedures over a 4-month period investigated the incidence of hypoxaemic events during anaesthesia for children requiring airway interventions. The results showed 27 of 87 children (34%) presenting for tubeless upper airway surgery experienced a hypoxaemic event with a desaturation event to less than 90% during the surgical procedure. Twenty-three per cent of these children with a hypoxaemic event required surgical interruption and a rescue oxygenation by positive pressure ventilation. Assuming 90% power to demonstrate a difference between HIGH-FLOW and standard technique with a reduction of the primary outcome from 23% to 11.5%, and a type 1 error rate of 0.05, we require a total sample size of 530 patients (15% attrition included). No interim analysis will be performed.

Statistical analysis plan

Descriptive statistics will be used to report on the baseline characteristics of the total study cohort and each subgroup, as well as by site. The primary and secondary outcome measures investigating clinical treatment failure will be compared using a χ^2 test, and the absolute difference between treatment groups will be reported as the risk difference, 95% CI and p value. Analysis will be by intention to treat. For continuous parameters, an independent t-test will be used assuming normal data distribution. Statistical significance will be set at the 0.05 level. Post-hoc power analyses may be undertaken to determine if results found in subgroup analyses (defined a priori; age group <1 year, patients with SpO_2 <80% during rescue attempt) are reliable. The statistical analysis plan will be published with the protocol in an open-access journal.

Recruitment, randomisation, allocation concealment and blinding

Consecutive elective cases for tubeless upper airway surgery will be screened for eligible participants. Patients booked for these procedures will be screened and recruited for inclusion in the study against the inclusion and exclusion criteria by the chief investigator or clinical research assistant. A screening log will be used to capture eligibility data. Patients will be allocated to a treatment arm using a web-computer-based randomisation schedule and an allocation of 1:1 per treatment arm. Randomisation will be stratified by site and age (<1 year, 1–5 year and 5–16 year of age), with randomly varied block sizes[3 5 7 9] within each stratum. Patients will be allocated to a study arm immediately after consent has been achieved to allow enough time to prepare the relevant equipment and drugs for anaesthesia. The equipment for both techniques will be set up prior to commencement of the list to not compromise the theatre work flow. It is not possible to blind anaesthetists or outcome assessors to treatment allocation due to the nature of the intervention.

Study procedures

Baseline and outcome parameters will be collected by a dedicated research nurse. Patient demographics will include age, weight, American Society of Anesthesiology status, comorbidities including recent lung pathologies and preoperative oxygen or ventilatory support, diagnosis, preceding procedures including flexible bronchoscopy

±BAL and surgical procedure. Number of rescue oxygenation attempts and interruption of the surgical procedure to correct hypoxaemia will be recorded. Additionally, all relevant data to capture the secondary outcomes will be noted. Clinical parameters throughout the entire procedure from induction to end of anaesthesia: baseline and 5 min intervals SpO_2, heart rate (HR), respiratory rate (RR), non-invasive blood pressure (NIBP), end tidal CO_2 (for HIGH-FLOW preapplication of cannula and post procedure), length of procedure, fresh gas flow rate. $TcCO_2$, O_2 and saturations will be acquired via TCM Flex Monitor (Radiometer, Copenhagen, Denmark) and the ORI will be measured with Radical-7 (Masimo, Irvine, California, USA). The $TcCO_2$ and ORI measurement, however, will remain blinded for the operator. All continuous physiological parameters will be integrated with the ICM+software (Cambridge University, UK). All physiological data will be analysed by the study engineer, who will also remain blinded for the intervention applied.

Cormack and Lehane classification on direct laryngoscopy will be noted and length of stay in postanaesthetic care unit or PICU. Continuous standard monitoring including HR, SpO_2 averaged to 5 seconds, non-invasive blood pressure at 5 min intervals, RR and ECG will be established at induction of anaesthesia and displayed by Phillips monitors as is routine anaesthetic practice.

Data collection and management

Data will be entered onto the case report form directly from the source data using the electronic data platform REDCap (Research Electronic Data Capture, Vanderbuilt; http://project-redcap.org/) V.7. All theatre lists including upper airway surgeries will be screened for eligible patients. A screening log will record patient information including: name, unique reference number, eligibility, enrolment and treatment allocation. Demographic variables to be collected include age, sex, weight, ASA score, diagnosis, date, preoperative ventilatory support and comorbidities including recent lung pathology. All data will be deidentified and confidentiality of all medical record information preserved. A protocol deviation will be defined as 'the incorrect intervention was used for a portion of study enrolment'.

Patient follow-up to assess long-term impact

Semistructured surveys and questionnaires using validated tools will be undertaken to assess quality of life and functional status. Assessment will be prospectively performed at randomisation and hospital discharge using Functional Status Score, Paediatric Overall Performance Score[9] and Paediatric Quality of Life.[10] Families will be contacted again at 6 months post randomisation by the study nurse with the print or electronic questionnaires. For neurocognitive and behavioural assessment of children<5 years, Ages and Stages Questionnaire and the Vineland assessment tool will be used.[11] For children≥5 years, the Behaviour Rating Inventory of Executive Function and the Vineland assessment tool will be used. Parents will be contacted by letter, email and phone to maximise response rate, aiming at >80% response rates. Questionnaires will assess functional status in the domains, such as communication, gross motor skills, fine motor skills, problem solving and interpersonal/social skills. Moderate neurocognitive impairment will be defined as a scores <-1 and −2 SD below the mean, in at least one of the five domains. Severe neurocognitive impairment will be defined as a scores <-2 SD below the mean, in at least one of the five domains. Subanalyses will examine a number of domains with moderate or severe impairment, and average scores. Analyses will be adjusted for comorbidity, age and socioeconomic status.

Patient and public involvement

Due to the nature of the study and the recruitment of young patients (18 years), patients and their parents and or guardians were not involved in the development of the research question or study protocol. The results of the study will be disseminated to study participants who provide an email on the consent document in the form of a short summary of study findings.

Ethics and dissemination of results

Ethics

Ethics approval was sought and obtained for the HAMSTER Trial from Children's Health Queensland HREC/18/QRCH/130 (Appendix I, approved consent form). Informed prospective and written consent from all patient representatives will be obtained prior to study enrolment. For children older than 10 years, additional child-specific assent will be obtained.

Dissemination

The Standard Protocol Items: Recommendations for Interventional Trials[12] explanation and elaboration: guidance for protocols of clinical trials and The Consolidated Standards of Reporting Trials (CONSORT) to guide protocol and study design.[12 13] All dissemination will involve aggregate data only and be undertaken using the CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials[14] and the template for intervention description and replication checklist.[15]

Trial status

Recruitment of patients to HAMSTER commenced in September 2018, 80 children have been recruited. We expect to complete recruitment in 2 years.

Trial endorsement

This trial has received Australian and New Zealand College of Anaesthetist Clinical Trial Network endorsement April 2019.

DISCUSSION

This multicentre RCT will determine the evidence of superiority of HIGH-FLOW compared with LOW-FLOW to reduce hypoxaemic events requiring interruption

for rescue oxygenation during anaesthesia for children with abnormal airways requiring tubeless upper airway surgery. This study will also provide data of significant adverse cardiorespiratory events, PICU admission and length of hospital stay. High-quality evidence derived from a full efficacy trial will enable the successful translation and adoption of this new technique into paediatric anaesthesia practice and will answer important aspects of clinical and cost effectiveness.

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Contributors SH, JT and AS conceived the study, developed the protocol. SH and AS wrote funding applications, drafted and revised the final manuscript. TW completed ethics and governance applications. BSvU-S, PS, DS, JS, SV, FT, AD, NS, HB, LB and BH assisted with protocol development and revised and approved the final manuscript. KG contributed to statistical methods, funding applications and revised and approved the final draft. MS contributed to health economics.

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Competing interests SH and AS have received support by Fisher & Paykel Health Care for travel and accommodation to attend conferences.

Patient consent for publication Not required.

Ethics approval The study protocol has been reviewed and approved by local ethics committee (Children's Health Queensland Human Research Ethics Committee) (HREC/18/QRCH/130 latest approved version 5).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement There are no data in this work.

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