CLINICAL STUDY PROTOCOL

R&D registration number = **14SG04**

Title

Correlation of nasopharyngeal and lower oesophageal temperatures in children ventilated with an endotracheal tube with leak

Purpose

Non-commercial study to find agreement between methods

Study investigators

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Background

During surgery under general anaesthesia a patient tends to cool down due to radiation, convection, evaporation and conduction (1). Under anaesthesia a patient loses their ability to regulate their own body temperature and solely relies on the anaesthetist to control their temperature with warming and cooling devices. Perioperative hypothermia is known to cause multiple complications such as surgical wound infection, coagulopathy, prolonged drug metabolism, shivering and increased oxygen consumption, all of which can affect patient outcome (2). However, hyperthermia in children also comes with risks such as febrile seizures or increased metabolic activity, so it is important to find a balance of maintaining normothermia (36.5˚C to 37.5˚C) accurately. In order to achieve this, temperature is routinely monitored under anaesthesia. NICE guidelines (3) recommend that temperature be monitored at least every 30 minutes. Continuous temperature monitoring devices such as those based on a thermistor design are commonly placed by anaesthetists, and indeed anaesthetic machines are routinely equipped to be compatible with this technology. NICE also recommends that when using a device to measure temperature, anaesthetists should be aware of adjustments that may need to be made to estimate core temperature from recorded temperature. Different sites of temperature measurement correlate to varying degrees with actual core temperature. Measuring core temperature in the patient's heart is the gold standard upon which to base decisions regarding temperature management, but measurement is invasive with a risk of complications (4) and is thus inappropriate in the vast majority of cases. Therefore alternative sites are generally used as surrogates of core temperature and it is important to identify a site that precisely reflects temperature of the core.

Oesophageal temperature accurately reflects core temperature (5) when a probe is positioned in the lower oesophagus (excluding open heart or lung surgery). However, the position of this probe must accurately be in the lower third of the oesophagus, lest a higher location is influenced by the cooler tracheal temperature (6-9). Compared to an adult, the short distance between the stomach, lower and middle oesophagus in a child makes reliable placement challenging. In order to achieve the precise placement of oesophageal temperature probes in adults and children, some formulas (10, 11) have been devised with varying success but none is perfect and accurate oesophageal temperature probe placement remains elusive, limiting the usefulness of the site.

The nasopharynx receives a good blood supply via the external carotid artery and therefore could correlate well with core temperature. The nasopharyngeal temperature probe confers the advantage of simplicity of placement compared to its oesophageal counterpart. The value of nasopharyngeal temperature's correlation with that of the core is generally regarded as accurate (12-14) in adults. In children undergoing anaesthesia often uncuffed endotracheal tubes are utilized, as historically in paediatric anaesthesia there have been concerns about subglottic stenosis and postoperative stridor (15) but to date there is no evidence that newer Microcuff® tubes are any less safe in children than uncuffed tubes (19). The use of uncuffed tubes is in direct contrast to adults, in whom cuffed endotracheal tubes are placed by anaesthetists. In the paediatric population very little evidence exists, although in small, poor quality trials findings are favourable for nasopharyngeal temperature comparisons to core (16). When a patient is ventilated during general anaesthesia, a humidity and moisture exchange filter (HMEF) assists in warming inspired gases administered from an anaesthetic machine, but does so incompletely (not achieving body temperature). With an uncuffed

endotracheal tube an escape of ventilated gases from the trachea upwards towards the mouth and nose occurs via the nasopharynx. With a temperature that is lower than body temperature, even at low flows, (17) these gases could possibly have a cooling effect on temperature in the nasopharynx (18). The question remains, thus, whether or not nasopharyngeal temperature is influenced by the cooling effects of these escaped gases or not.

Study objectives

This study will seek to find an agreement of methods (lower oesophageal and nasopharyngeal sites) to measure temperature in children undergoing general anaesthesia with an endotracheal tube that has a leak. This is an important question to answer because it is not known whether or not oesophageal and nasopharyngeal temperatures correlate in children ventilated with an uncuffed endotracheal tube, and would allow clinicians to confidently use the more feasible nasopharyngeal temperature probes if this were the case.

Study Design

Prospective, unblinded, cross-sectional (observational) agreement study

Approval will be obtained from the Research Ethics Committee

Written parental informed consent will be obtained prior to investigation. Parents will be informed of their right to withdraw at any stage of the trial without compromising their clinical care.

Inclusion criteria

Age: 8 months to 7 years

Patient requires general anaesthesia with endotracheal intubation for a procedure assisted by radiography (e.g. line insertion, line change)

Patient requires chest radiograph for procedure

Expected anaesthetic time more than 30 minutes

Exclusion criteria

No written parental written consent

Known oesophageal pathology (e.g. tracheo-oesophageal fistula, oesophageal strictures, oesophageal varices, oesophageal atresia)

Known base of skull or midface fractures

Previous gastric bypass surgery or nasal surgery

Known coagulopathy

Previous alkaline ingestion

High aspiration risk

Significant respiratory co-morbidity requiring anticipated peak airway pressures > 25 cmH_2O

ASA 4 – 5

Tracheostomy in situ

Severe sepsis or septic shock or other other condition (such as bronchopulmonary fistula) that precludes use of tidal volume ventilation over 7 ml/kg

Known airway abnormalities (e.g. subglottic stenosis) that preclude placement of a MicroCuff® endotracheal tube

Oesophageal or nasopharyngeal probe contraindicated for reasons related to surgery / procedure

Feasibility of study/ number of patients

Statistical advice and analysis has been sought from the Great Ormond Street Hospital/ Institute for Child Health (ICH) statistical support team. 100 patients would suffice to be able to estimate agreement between methods, giving a 95% CI about +/- (0.34 x standard deviation).

At GOSH approximately 1500 radiography-assisted procedures are performed on children annually. Of these it is estimated that about 1000 are performed on children between the ages of 8 months and 7 years old. Of these it is anticipated that about 750 would meet inclusion criteria without exclusion criteria, meaning that this study would be suitable for a single centre (GOSH).

Patient management and intervention

Patient management for general anaesthesia will continue according to usual paediatric anaesthetic standards. Anaesthesia will be induced by an intravenous or inhalational method. After administration of muscle relaxant, the patient will be intubated with a cuffed MicroCuff® endotracheal tube, which has been shown to be safe in children (19) and is even recommended by some experts as superior to an uncuffed endotracheal tube (20).

The size of the low-pressure, high-volume endotracheal tube shall be determined according to manufacturer's instructions (21). The anaesthetist will confirm the presence of an audible leak at <15 cmH_2O pressure as is typical in paediatric anaesthesia, and in the unlikely event that this does not exist then the endotracheal tube will be changed to one size smaller. Once a leak has been confirmed the cuff of the endotracheal tube will be inflated under guidance of a cuff manometer. The in-built ventilator's spirometric equipment will be used to measure expired tidal volumes and these will later be compared to set inspired volume to calculate the leak during cuff deflation.

An oesophageal and nasopharyngeal temperature probe will be inserted prior to commencement of the actual procedure (after anaesthesia has been established). The insertion depth of the nasopharyngeal probe will be estimated by a formula previously described (9):

Length (cm) = (distance from tragus to nostril) – 2

This length will then be adjusted at the discretion of the operator inserting the probe in order to achieve the level of the posterior border of the soft palate (position confirmed with laryngoscope).

The oesophageal probe will initially be inserted to a depth determined by a formula slightly adjusted from a previously described method to calculate the distance to the lower oesophageal sphincter in children (22):

Length (cm) = (0.226 x height) + 5

Once the initial radiograph has been taken (timing of which shall be dictated by the surgical team as this radiograph will assist with the procedure), the intervertebral space between the 8^{th} and 9^{th} thoracic vertebrae will be identified and the distance between the end of the oesophageal probe and this landmark will be measured. The position of the end of the temperature probe will be adjusted to the level of T8/ T9, which corresponds to the lower third of the oesophagus.

The anaesthetic gas mixture flow will be set at 2L /min in order to standardize the flow of this potentially cooling factor between patients. The anaesthetist will set the ventilator mode to volume control ventilation (VCV) without leak compensation with a Peak End Expiratory Pressure (PEEP) of 5 and a tidal volume of 7 – 9 ml/kg. The inspiratory: expiratory (I:E) ratio will be set to 1:2. Approximately 1 minute following satisfactory positioning of the temperature probe, the temperature of the oesophageal and nasopharyngeal probes will be recorded over a period of 20 breath cycles (approximately 1 minute), while the ventilator's

spirometric equipment will be utilized to measure expired tidal volume and peak airway pressure..

The endotracheal tube cuff will now be deflated to allow an anaesthetic gas leak, thus simulating the use of an uncuffed endotracheal tube. The volume of air in the cuff will be adjusted by the anaesthetist to achieve a clinically soft audible leak (whilst on the ventilator). Temperature and spirometry measurements will recommence approximately 1 minute hereafter (simulating an uncuffed endotracheal tube scenario), again over a period of 20 breath cycles. Once this is completed the anaesthetist will use their discretion whether or not they wish to fully re-inflate (with cuff manometry) the endotracheal tube cuff or not for the remainder of the procedure.

As is usual during anaesthesia, standard body warming measures (aiming for normothermia) will be taken, guided by the measured temperatures.

Data collection

The following data will be collected:

Demographics – including date of procedure, date of birth, age, height, ASA status

Initial distance that oesophageal probe is inserted, based on formula described above

Distance of oesophageal probe tip away from T8/T9 intervertebral space

Temperature of nasopharyngeal probe at a point approximately 1 minute after satisfactory positioning at T8/T9 level and again 1 minute after cuff deflation to a clinically soft audible leak

During the periods of cuff inflation as well as cuff deflation, inspired and expired tidal volumes will be measured by spirometry over a 20 breath cycle, and these will later be used to calculate Fractional volume loss (FVL).

Ventilator settings including I:E ratio, PEEP, Peak AirWay Pressure (PAWP)

Distance of nasopharyngeal probe insertion

Complications of nasopharyngeal probe insertion (bleeding, failure)

Complications of oesophageal probe insertion (failure)

Cuff pressure utilized

Duration of study

It is estimated that about 1000 radiography-assisted procedures are performed annually on children between the ages of 8 months and 7 years old at GOSH. Of these, it is anticipated that about 750 would meet inclusion criteria without exclusion criteria. If a parental consent rate of 50% is achieved, then the study would estimate to run for 6 months (allowing for 40% of patients missed due to researcher unavailability) in order to recruit 100 patients.

Risks of study

Recruitment of patients will include only those who would anyway have received an endotracheal tube for anaesthesia (as opposed to an alternative anaesthetic airway such as a supraglottic airway device). The study population will be those children undergoing a procedure that requires radiography (e.g line insertion) ie there is a need for X-rays for surgical reasons. These X-rays will simultaneously be used to confirm optimal oesophageal probe position, and no radiation risk will be added for probe X-ray. Position will initially have been estimated with a formula and adjusted according to radiograph.

It is usual in anaesthesia to measure temperature intraoperatively, and common practice is to use a nasopharyngeal (23) or oesophageal probe when anaesthesia is expected to last longer than 30 minutes (24). As nasopharyngeal and oesophageal temperature probes are commonly inserted during general anaesthesia (25-27), practice will be little changed from standard during this study. Children will be recruited if they are expected to undergo anaesthesia for greater than 30 minutes. Insertion of an oesophageal temperature probe as well as a nasopharyngeal probe is expected to add only 1 minute to total anaesthetic time, meaning that the child will be kept asleep only fractionally longer than would otherwise have been the case if they were not recruited into the study. This short prolongation of anaesthesia will not have any significant clinical effects.

The insertion of a nasopharyngeal temperature probe can cause nasal bleeding (28) but this is self-limiting in the overwhelming majority of cases. Those with a known coagulopathy will not be recruited into this study due to risk of nasal bleeding. Failure to insert a nasopharyngeal probe can occasionally occur, for example due to previous nasal trauma, in which case success in the other nare is usually possible. Very rarely will a nasopharyngeal probe be unable to be inserted in both nares, in which case recruitment of the patient into the study will be abandoned. There is a possibility that the nasopharyngeal probe will be placed too deep, reaching the mouth. In this case, there is a possibility that ambient temperature may reduce the recorded temperature, causing inaccuracy. This risk will be minimized by the insertion of the temperature probe being done by the researchers, aiming to insert the probe's end to the level of the posterior border of the soft palate (under laryngoscopic view after estimating depth required by formula). Very rarely have other complications occurred with nasopharyngeal probes, including one case report relating to too deep insertion of nasopharyngeal probe during surgery on the oesophagus (29) and a report on defective nasopharyngeal probes (30), both scenarios of which are highly unlikely to be relevant in our proposed study.

The insertion of the oesophageal probe is a safe procedure, with very few side-effects reported in the literature. Rarely has an oesophageal temperature probe been inadvertently inserted intratracheally (31). If this were to occur, early diagnosis would be possible due to accompanying radiography, noting the probe to cross the carina. Rarely will oesophageal probe insertion fail, in which case recruitment into the study will terminate.

Statistics and data analysis

We consider a clinically unacceptable difference as a difference of greater than 0.5˚C between methods.

The study recruitment rate will be assessed by recording patients successfully entered into the study as well as those for whom parental consent was not achieved. Demographic data will be appropriately recorded and analysed in terms of means and medians. Temperature measurements with the oesophageal probe will be compared to temperature measurements with the nasopharyngeal probe and mean differences, standard deviations, and 95% confidence intervals will be calculated and tabulated. Bland-Altman plots of the esophageal-nasopharyngeal temperature differences will be drawn. Differences will be checked for normality. Differences against mean will also be checked for variability (making sure that differences do not increase with mean). Linear regression analysis shall be utilized with scatter plot diagrams and r values calculated. A paired t-test will be performed to exclude systematic bias. Endotracheal leak, as measured by spirometry and fractional volume loss, will be measured, analysed and tabulated for means and standard deviations. It is anticipated that a clinically audible leak will correspond to a FVL of approximately 12.4 – 29.3% (based on data received directly from study author regarding IQR from a previous study (32)) for 50% of patients.

After the study has been completed we also plan to do a subgroup analysis for agreement between methods on 2 subgroups of patients: (1) those with FVL < 21.1% (2) those with FVL > 21.1%. This is in order to determine if there is any potential effect of leak size that might affect temperature differences.

Data handling

After parental written consent on recruitment, a data form with study number will be used (no hospital number or name of patient). Once completed, these patient data forms will be securely stored in a filing cabinet in the Anaesthetic office (access to which is controlled by GOSH swipe card). Each form will also be scanned and stored into a password-protected folder on the GOSH intranet “i drive”. Patient confidentiality will be ensured at all stages.

Study finances & disclosures

In order to meet the costs of consumables that would not routinely otherwise have been used in normal clinical management:

For oesophaegeal temperature probes: 100 probes would cost £330.70

For MicroCuff® endotracheal tubes: 100 tubes would cost £600

The cost for uncuffed Portex tubes that would otherwise have been used anyway is £123

We expect a possible extra 10% of consumables to be used for patients that might be recruited into the trial but are unable to complete the trial.

Total required = (110% x £993.70) - £123 ≈ £900

Further savings will also occur due to minimal use of sevoflurane.

Discussions have taken place within the anaesthetic department (via the clinical lead in anaesthesia Dr Scuplak) and funding has been internally arranged.

No authors shall be remunerated for their efforts and no conflicts of interest are declared.

Representatives from Covidien and Philips assisted in education of study authors regarding recording and retrieving temperature data

Publication plan

Following the study, the findings will be submitted to journal editors for consideration for publication in a peer-reviewed journal. Failing that, submissions will be made to conference or congress organisers with a view to present the findings in poster or oral presentation format. Raw data will be safely stored so that any potential future investigators can have access to this.

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