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Study to assess the laryngeal and pharyngeal spread of topical local anaesthetic administered orally during general anaesthesia in children.

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Pediatric Anesthesia

Study to assess the laryngeal and pharyngeal spread of topical local anaesthetic administered orally during general anaesthesia in children.



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Cover Letter

Please consider the following paper for re-submission to Pediatric Anesthesia.

The enclosed manuscript has been read and approved by all authors, it is not under active consideration for publication elsewhere, has not been accepted for publication, nor has it been published in full or in part.

Yours faithfully,

R Beringer

For Peer Review

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3 Study to assess the laryngeal and pharyngeal spread of
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7 topical local anaesthetic administered orally during
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10 general anaesthesia in children.
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39 Running title: Topical anaesthesia of the paediatric airway
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COVER SHEET: CO-AUTHOR DETAILS

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For Peer Review

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3 Abstract:
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8 *Background:* Topical local anaesthesia of the airway of anaesthetised children
9
10 has many potential benefits. In our institution, lignocaine is topically instilled
11
12 blindly into the back of the mouth with the expectation that it will come into
13
14 contact with the larynx. The volume and method of application varies between
15
16 clinicians. There is no published evidence to support the plausibility of this
17
18 technique.
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24 *Aim:* To determine whether this technique of instillation results in the local
25
26 anaesthetic coming into contact with key laryngeal structures and whether this
27
28 is influenced by volume or additional physical manoeuvres.
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34 *Methods/Materials:* Sixty three healthy anaesthetised children between six
35
36 months and 16 years old had lignocaine stained with methylene blue poured
37
38 into the back of their mouths. The volume and subsequent physical
39
40 manoeuvre were determined by randomisation. A blinded observer assessed
41
42 staining of the vocal cords, epiglottis, vallecula and piriform fossae by direct
43
44 laryngoscopy. Airway complications were recorded.
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50 *Results:* Fifty three of the 63 children had complete staining of all four areas.
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52 Four children had one area unstained and all others had at least partial
53
54 staining of all four structures. Nine children coughed following induction of
55
56 anaesthesia. Coughing was more likely in children with incomplete staining
57
58 ($p=0.03$), low volume lignocaine ($p=0.003$) and following a head lift ($p=0.02$).
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6 *Conclusion:* Oral administration of lignocaine without use of a laryngoscope
7
8 frequently results in widespread coverage of key laryngeal structures and may
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10 reduce the risk of coughing.
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For Peer Review

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3 Introduction:
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8 Applying local anaesthetics topically to the airway of anaesthetised patients
9 has many potential benefits such as: reducing the incidence of coughing and
10 laryngospasm on induction or emergence from general anaesthesia (1-3),
11 improving conditions for tracheal intubation in the absence of neuromuscular
12 blockade (4), reducing the frequency of postoperative sore throat (5) and
13 attenuation of the sympathetic nervous system response to intubation (6-9).
14
15 Lignocaine is the most frequently used local anaesthetic agent for this
16 purpose. It has been shown to be beneficial when used topically or
17 systemically, but the evidence suggests a superior effect from topical use,
18 with a lower total dose and lower systemic blood concentration (8).
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34 These advantages must however be balanced by the potential risk to a child
35 with a topically anaesthetised and unprotected airway, for example following
36 extubation. Although there is no published literature to support a significant
37 risk of aspiration in this situation, care must be taken with looking after a child
38 with obtunded protective reflexes.
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48 The most frequently described method for topical application of lignocaine is
49 to spray it onto the laryngeal and tracheal mucosa under direct vision. An
50 alternative technique has evolved in our institution, in which the local
51 anaesthetic is blindly instilled into the back of the mouth, with the expectation
52 that it will anaesthetise the hypopharynx and proximal laryngeal structures.
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60 This practice has some variations including use of different volumes of local

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3 anaesthetic as well as occasional use of additional procedures such as lifting
4 the patient's head, or posterior depression of the larynx (dunking) with the
5 intention of enhancing delivery of the solution to the desired anatomical
6 structure. The advantages of this technique include simplicity, and avoidance
7 of the need for laryngoscopy to allow application of the local anaesthetic.
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10 Laryngoscopy is a potent cause of sympathetic stimulation and is also
11 associated with adverse reflexes such as laryngospasm and coughing. It is
12 therefore best performed once the airway has been anaesthetised. Review of
13 the published literature does not reveal any previous studies assessing the
14 use of local anaesthetic in this way. There is therefore some uncertainty if this
15 practice is clinically effective, or if it is even plausible that the local anaesthetic
16 reaches the area of intended action.
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34 In this study we added a dye (methylene blue) to the local anaesthetic and
35 observed the degree of staining of the laryngeal structures. The purpose of
36 this study was to gain evidence regarding the plausibility that this technique
37 could anaesthetise the airway. In addition we wished to identify whether
38 factors such as volume of local anaesthetic or additional physical manoeuvres
39 influenced whether the local anaesthetic reached the intended site of action.
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48 By determining if the local anaesthetic does indeed reach the relevant
49 structures, this could inform future practice, and provide the scientific
50 plausibility for further study to examine the effectiveness of the technique in
51 terms of relevant clinical outcomes.
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METHODS

After obtaining parental consent and approval from the Human Research Ethics Committee at the Royal Children's Hospital in Melbourne, we recruited sixty three healthy children (ASA 1 or 2), aged between 6 months and 16 years, who were scheduled to undergo elective surgery for which they would require a tracheal tube. Children with a contraindication to the use of either of the study drugs, or an anticipated difficult laryngoscopy were excluded.

Children were stratified into five age groups (6 to 12 months; 1 to 2 years; 2 to four years; 4 to 8 years; and 8 to 16 years) and randomised to receive one of two volumes of lignocaine (0.05 or 0.15 ml/kg), and one of three additional manoeuvres following application of the local anaesthetic (no additional manoeuvre; head lift; or laryngeal dunk). Head lift was performed by lifting the child's head until the chin touched the chest for three seconds and then returning it to the neutral position. Laryngeal dunk was performed by applying standard cricoid pressure for three seconds. Methylene blue was mixed with the lignocaine to act as a tissue stain. Two percent lignocaine was mixed with 1% methylene blue in a 9:1 ratio by volume, resulting in a solution containing 1.8 percent lignocaine and 0.1 percent methylene blue. A maximum volume of four millilitres was used.

The primary outcome measure was complete staining of four laryngeal structures: the vocal cords; piriform fossae; epiglottis; and vallecula. The secondary outcome measure was the frequency of airway complications after

1
2
3 instillation of the dye up until the start of surgery, including: coughing;
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5 laryngospasm; oxygen desaturation (below 90 percent); and bradycardia (less
6
7 than 80 percent of baseline rate).
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12 All observations during the study were made by one of two principal
13
14 investigators. The choice of anaesthetic technique was decided by the
15
16 anaesthetist. Once the patient was anaesthetised, one investigator poured the
17
18 predetermined volume of lignocaine/methylene blue into the back of the
19
20 child's mouth over a few seconds using a syringe without needle and
21
22 performed any additional manoeuvre required by randomisation. The
23
24 facemask was then reapplied to the child's face and the child ventilated or
25
26 allowed to breathe as normal. When the anaesthetist was satisfied that the
27
28 child was adequately anaesthetised to allow intubation, the other blinded
29
30 investigator performed standard direct laryngoscopy to assess the staining of
31
32 the vocal cords, epiglottis, vallecula and piriform fossae. Staining was
33
34 classified as complete, partial or unstained. The investigator or anaesthetist
35
36 then inserted the tracheal tube and surgery commenced as normal. The
37
38 degree of staining was recorded on a case report form along with
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40 demographic information, details of the anaesthetic technique and details of
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42 adverse events.
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51 52 53 *Sample size and statistics* 54 55

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58 This was a prospective, randomised, blinded, observational study. We initially
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60 intended to recruit a total of 120 patients. This would have resulted in 24

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3 children in each age group; 60 children for each volume of lignocaine; and 40
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5 children for each additional manoeuvre. However, recruitment was slower
6
7 than expected and after studying 63 children the principal investigator's
8
9 rotation at the hospital came to an end. It was therefore decided that the study
10
11 should be stopped at this stage. The analysis plan was to report the frequency
12
13 of full staining in each combination group and depending on the spread of
14
15 results, perform more sophisticated post-hoc analysis examining the
16
17 difference between groups if possible. Such post-hoc analyses were
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19 performed using the Chi squared test, with Yates' correction for continuity
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21 when expected frequency was less than five.
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RESULTS

Sixty three children were recruited. More children were recruited from the older age groups, but otherwise the groups were well balanced (Table 1). Age ranged from seven months to 15 years, and weight ranged from seven to 109 kilograms. In the five different age groups (six to 12 months; 1 to 2 years; 2 to 4 years; 4 to 8 years and 8 to 16 years) there were 6; 6; 7; 21 and 23 children respectively. In the low volume and high volume groups, there were 31 and 32 children respectively. For the different techniques (no additional technique; head lift and laryngeal dunk) there were 21; 20; and 22 children respectively. No substantial differences were noted between the groups in terms of patient demographics or anaesthetic technique, including use of muscle relaxation. The time between instillation of solution and laryngoscopy ranged from 30 seconds to four minutes (median time one minute).

The primary outcome measure was complete staining of four laryngeal structures (vocal cords, piriform fossae, epiglottis and vallecula). Fifty three of the 63 subjects had complete staining of all four areas. Four children had one area unstained and all others had at least partial staining of the four structures. All children had complete staining of the piriform fossae. Eight children had only partial staining of the epiglottis, one child had an unstained vallecula and three children had no staining of the vocal cords. The details of the 10 children in whom there was incomplete staining are shown in Table 2.

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3 Quantitative analysis of the differences in the degree of staining between the
4 different subgroups using the Chi squared test with Yates correction for
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6 continuity revealed no evidence for differences between: the five age groups
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8 (p=0.9); the two different volumes (p=0.3); or the use of additional techniques
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10 (p=0.9).
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17 The secondary outcome measure was the frequency of adverse events during
18 induction of anaesthesia (cough, laryngospasm and drop in oxygen saturation
19 below 90 percent). Nine children coughed, two during intubation and seven
20 following intubation. No children developed laryngospasm or bradycardia.
21
22 Two children desaturated below 90 percent, although in both cases this was
23 attributed to anaesthetic technique, not an airway complication. Details of the
24 nine children who coughed are shown in Table 3. Coughing was more likely in
25 children with incomplete staining (five of the 53 children with complete
26 staining and in four of the 10 children with incomplete staining; risk ratio 0.24;
27 95% confidence intervals 0.08 to 0.7; p=0.03). All nine children who coughed
28 had received the low volume of lignocaine (p=0.003). Coughing occurred in
29 seven children who had received a head lift, none who had received a
30 laryngeal dunk and two patients in which no additional technique was used
31 (p=0.02).
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53 Follow up of children after their procedure revealed no complications apart
54 from temporary residual oropharyngeal staining. There were no reported
55 episodes of aspiration or difficulty with drinking or eating in the postoperative
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60 period.

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3 DISCUSSION
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8 These results demonstrate that oral administration of lignocaine without use of
9 a laryngoscope frequently results in complete coverage of key laryngeal
10 structures. Fifty three of 63 children had completely stained larynxes from this
11 technique, and the other 10 children all had at least partial staining of the
12 larynx.
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22 The standard method of topically anaesthetising the airway is to spray local
23 anaesthetic onto the larynx under direct vision using a laryngoscope. This
24 might result in more frequent complete coverage than was demonstrated by
25 this study, and therefore may be the technique of choice when local
26 anaesthesia is absolutely necessary. However, laryngoscopy is not without
27 risks and is associated with coughing, laryngospasm and regurgitation as well
28 as stimulation of the sympathetic nervous system. A major potential benefit of
29 the technique used in this study is to reduce the complications of
30 laryngoscopy by providing anaesthesia before the laryngoscope comes into
31 contact with the patient. Supplementary spraying of the trachea under direct
32 vision may then be appropriate for some patients, such as those undergoing
33 bronchoscopy. The observation that staining was extensive suggests it is
34 plausible that the technique we use could be as effective as spraying under
35 direct vision.
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57 We wanted to identify whether factors such as volume of local anaesthetic or
58 additional physical manoeuvres influenced whether the drug reached the
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3 intended site of action. No significant associations were observed with
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5 regards to staining of the larynx. However, the small numbers limit the power
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7 of this analysis.
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12 Complications related to airway instrumentation during this study were a
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14 secondary outcome measure and relatively few in number, so it is difficult to
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16 draw firm conclusions. However, there was evidence for an association
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18 between both volume and technique, and coughing on induction. There was
19
20 also evidence for an association between degree of staining and coughing.
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22 Coughing was more frequent in patients with incomplete coverage of the
23
24 larynx, only occurred in patients who received the lower volume of lignocaine
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26 and was also associated with the use of head lift after administration of
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28 lignocaine. These findings would support using the higher volume of local
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30 anaesthetic and avoiding head lift in future practice.
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39 The observation that topical lignocaine reduces risk of coughing is consistent
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41 with the findings of other investigators who have shown reduced frequency
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43 and severity of coughing for up to two hours following application of topical
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45 lignocaine (1). It seems plausible that by reducing the frequency of coughing,
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47 this technique may also reduce the frequency of more severe complications
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49 such as laryngospasm. Further study is necessary to determine whether this
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51 is the case.
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57 The study has some limitations. The most significant is that staining does not
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59 necessarily equate with sufficient local anaesthesia to reduce reflex coughing
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3 or other responses to tracheal intubation. Although, as mentioned above we
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5 found evidence for some associations between staining and coughing, the
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7 anaesthetic conditions such as use of agent and depth of anaesthesia were
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9 not controlled at this period. These could influence any observed association.
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12 In order to design a study to assess the effect of topical local anaesthetic on
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14 adverse reflexes during anaesthesia, it would be necessary to standardise the
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16 anaesthetic technique and also the time between instillation of local
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18 anaesthetic and laryngoscopy.
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25 There is a theoretical potential for physicochemical interactions between
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27 methylene blue and lignocaine which may have influenced the findings.
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29 Methylene blue is a weak acid (pH 3 to 4.5) and may alter the lipid solubility of
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31 lignocaine and the detergent effect of methylene blue may have enhanced the
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33 spread of the mixture over mucus membranes.
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39 The main disadvantage to using topical local anaesthetic within the airway is
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41 that persisting anaesthesia following extubation may make aspiration of
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43 pharyngeal contents more likely. There is little evidence in the literature to
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45 suggest that this is a significant problem, but it seems intuitive that the child
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47 with diminished protective reflexes may be at higher risk.
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53 In summary, this study supports the plausibility of this technique for topical
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55 anaesthesia of the larynx of anaesthetised children. This supports the
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57 continued use of this technique and we plan to carry out further research
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59 based upon these findings to determine whether this local anaesthesia of the
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paediatric airway improves actual clinical outcomes compared to other techniques.

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For Peer Review

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Table 1
Randomisation details and degree of laryngeal staining

Age		Technique		Volume		Number of patients	
category	number of patients	category	number of patients	category (ml/kg)	number of patients	Incompletely stained	Completely stained
6 – 12 months	6	None	2	0.05	1		1
				0.15	1		1
		Head lift	1	0.05	1		1
				0.15	0		
		Laryngeal dunk	3	0.05	1		1
				0.15	2		2
1 -2 years	6	None	2	0.05	1	1	
				0.15	1		1
		Head lift	2	0.05	1		1
				0.15	1		1
		Laryngeal dunk	2	0.05	1		1
				0.15	1	1	
2 – 4 years	7	None	1	0.05	0		
				0.15	1	1	
		Head lift	3	0.05	2	1	1
				0.15	1		1
		Laryngeal dunk	3	0.05	2		2
				0.15	1		1
4 – 8 years	21	None	8	0.05	4		4
				0.15	4		4
		Head lift	6	0.05	3		3
				0.15	3	1	2
		Laryngeal dunk	7	0.05	3	1	2
				0.15	4		4
8 – 16 years	23	None	8	0.05	4		4
				0.15	4		4
		Head lift	8	0.05	4	2	2
				0.15	4		4
		Laryngeal dunk	7	0.05	3	2	1
				0.15	4		4

Table 2
Details of the 10 children with incomplete staining

Patient	Vocal cords	Piriform Fossae	Epiglottis	Vallecula	Age (years)	Volume (mL/Kg)	Technique
1	Complete	Complete	Partial	Complete	4-8yrs	0.15	HL
2	Complete	Complete	Partial	Complete	4-8yrs	0.05	LD
3	Complete	Complete	Partial	Complete	8-16yrs	0.05	HL
4	Complete	Complete	Partial	Complete	4-8yrs	0.05	HL
5	Complete	Complete	Partial	Complete	8-16yrs	0.05	HL
6	Complete	Complete	Partial	Complete	4-8yrs	0.15	None
7	Complete	Complete	Partial	Unstained	2-4yrs	0.15	LD
8	Unstained	Complete	Complete	Complete	8-16yrs	0.05	LD
9	Unstained	Complete	Complete	Complete	1-2yrs	0.05	None
10	Unstained	Complete	Partial	Complete	8-16yrs	0.05	LD

Table 3

Details of the nine children who coughed

Child	Age (years)	Volume (mL/Kg)	Staining	Technique
1	4 to 8	0.05	complete	None
2	8 to 16	0.05	incomplete	Head lift
3	4 to 8	0.05	complete	Head lift
4	8 to 16	0.05	complete	Head lift
5	2 to 4	0.05	complete	Head lift
6	8 to 16	0.05	complete	Head lift
7	1 to 2	0.05	incomplete	None
8	4 to 8	0.05	incomplete	head lift
9	8 to 16	0.05	incomplete	head lift

For Peer Review

CONSORT Statement 2001 - Checklist 
 Items to include when reporting a randomized trial

<i>PAPER SECTION And topic</i>	Item	Descriptor	Reported on Page #
<i>TITLE & ABSTRACT</i>	1	<u>How participants were allocated to interventions</u> (e.g., "random allocation", "randomized", or "randomly assigned").	2, 3-4
<i>INTRODUCTION</i> Background	2	<u>Scientific background and explanation of rationale.</u>	6-7
<i>METHODS</i> Participants	3	<u>Eligibility criteria for participants</u> and the <u>settings and locations where the data were collected.</u>	8
Interventions	4	<u>Precise details of the interventions intended for each group and how and when they were actually administered.</u>	8
Objectives	5	<u>Specific objectives and hypotheses.</u>	6-7
Outcomes	6	<u>Clearly defined primary and secondary outcome measures</u> and, when applicable, any <u>methods used to enhance the quality of measurements</u> (e.g., multiple observations, training of assessors).	8-9
Sample size	7	<u>How sample size was determined</u> and, when applicable, <u>explanation of any interim analyses and stopping rules.</u>	9-10
Randomization -- Sequence generation	8	<u>Method used to generate the random allocation sequence, including details of any restrictions</u> (e.g., blocking, stratification)	8
Randomization -- Allocation concealment	9	<u>Method used to implement the random allocation sequence</u> (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Randomization -- Implementation	10	<u>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</u>	9
Blinding (masking)	11	<u>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment.</u> If done, <u>how the success of blinding was evaluated.</u>	9
Statistical methods	12	<u>Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses</u> , such as subgroup analyses and adjusted analyses.	9-10
<i>RESULTS</i> Participant flow	13	<u>Flow of participants through each stage</u> (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. <u>Describe protocol deviations from study as planned, together with reasons.</u>	
Recruitment	14	<u>Dates defining the periods of recruitment and follow-up.</u>	
Baseline data	15	<u>Baseline demographic and clinical characteristics of each group.</u>	
Numbers analyzed	16	<u>Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat".</u> State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	
Outcomes and estimation	17	<u>For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision</u> (e.g., 95% confidence interval).	
Ancillary analyses	18	<u>Address multiplicity by reporting any other analyses performed</u> , including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	
Adverse events	19	<u>All important adverse events or side effects in each intervention group.</u>	
<i>DISCUSSION</i> Interpretation	20	<u>Interpretation of the results</u> , taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	
Generalizability	21	<u>Generalizability (external validity) of the trial findings.</u>	
Overall evidence	22	<u>General interpretation of the results in the context of current evidence.</u>	

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