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A RANDOMIZED CONTROLLED TRIAL COMPARING EFFICACY OF INTRACUFF 0.5% ALKALINIZED LIGNOCAINE, 0.5% LIGNOCAINE AND SALINE ON ENDOTRACHEAL TUBE INDUCED LARYNGOTRACHEAL MORBIDITY IN CHILDREN

Anaesthesiology

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ABSTRACT

Background and Objectives: Postoperative laryngotracheal (LT) morbidity remains a common problem despite ongoing advances. There is a paucity of studies in children comparing the incidence of postoperative LT morbidity after instillation of endotracheal tube (ETT) cuff with 0.5% alkalinized lignocaine, lignocaine and saline. Therefore, the current study was undertaken to compare the efficacy of intracuff 0.5% alkalinized lignocaine, 0.5% lignocaine and saline in reducing the incidence of postoperative LT morbidity.

Material and Methods: A prospective randomized controlled trial was conducted involving 120 pediatric patients aged between 5 – 12 years of American Society of Anaesthesiologists (ASA) grade I and II, undergoing elective surgery. Patients were randomized into three groups - Group S (n=40), Group L (n=40) and Group AL (n=40) on the basis of inflation of ETT cuff with saline, 0.5% lignocaine (0.5 ml of 2% lignocaine + 7.5 ml of normal saline) and 0.5% alkalinized lignocaine (2.5 ml of 2% lignocaine +7.5ml of normal saline followed by disposal of 0.5 ml mixed solution + 0.5% of 7.5% NaHCO3) respectively. Inflation was performed until a cuff pressure of 20-30 cm H20 was achieved. Postoperatively cough, sore throat, dysphonia, dysphagia, pain and nausea and vomiting were noted at 1, 8 and 24 hours.

Results: Demographic variables were comparable in all the three groups in terms of age, sex, weight and height. Intra cuff instillation of alkalinized lignocaine resulted in an increased incidence of smooth extubation in comparison to lignocaine and saline (p=0.001), with lignocaine being significantly better than saline. (p=0.001) It was noted that intra cuff instillation of alkalinized lignocaine was significantly better than lignocaine which was significantly better than saline in terms of reduction in the incidence of post extubation cough and sore throat at 1 and 8 hours and dysphonia at 1 hour after extubation. (p=0.001) Alkalinized lignocaine and lignocaine were significantly better than saline in the reduction of bronchospasm, laryngospasm and bucking, cough and sore throat at 24 hours and dysphonia at 8 and 24 hours after extubation but no difference was found between Group AL and L. No differences were observed among three groups regarding incidence of dysphagia, nausea / vomiting and pain at 1 hour, 8 hours and 24 hours following extubation.

Conclusion & Recommendation: Intracuff instillation of alkalinized lignocaine can be recommended in children aged 5 – 12 years for decreasing the incidence of laryngotracheal comorbidities.

KEYWORDS

Alkalinized lignocaine; Bronchospasm; Cough; Dysphonia; Laryngotracheal morbidity; Lignocaine; Sore throat

INTRODUCTION

Endotracheal intubation is one of the most commonly performed interventions, with an estimated incidence of 30% of total surgeries performed worldwide. [1] Significant progress has been made with regard to the endotracheal tube designs since the introduction of the red rubber tube by Sir Ivan Magill. Despite these advances postoperative laryngotracheal (LT) morbidity remains a common problem. This is defined as a group of airway complications associated with tracheal intubation or extubation after general anaesthesia. Symptoms result from mucosal injury or inflammation caused by airway instrumentation (i.e., laryngoscope and suctioning) or the irritating effects of a foreign object like endotracheal tube (ETT). [2] Postoperative sore throat (POST) is one of the most undesirable morbidities that occurs in approximately 50% or more of surgical patients. [3] During emergence from general anaesthesia, patients may experience vigorous post extubation coughing (PEC), agitation or restlessness which may increase intracranial, intra-thoracic or intra-abdominal pressure, resulting in bronchospasm, wound dehiscence and bleeding. [4] Other laryngeal complications such as hoarseness, dysphonia or dysphagia are also noted in the postoperative period. [5] Important causes for POST and PEC include usage of a large size ETT, non-lubricated ETT, non-humidified gases, nitrous oxide diffusion, overinflation of cuff and multiple intubation attempts. [6] Prevention strategies for POST and other LT morbidities include nonpharmacological approaches like smaller size ETT, use of low pressure high volume cuffs and other prophylactic interventions such as anti-inflammatory drugs, opioids, steroids, or local anaesthetics. [7-12] Lignocaine is one of the most commonly used drugs for preventing POST, and its efficacy was evaluated in a Cochrane review in 2009. [13] Lignocaine, when administered as a cuff inflation medium, helps protect the tracheal mucosa through its topical anaesthetic effect, and prevents the diffusion of nitrous oxide into the cuff. [14] Alkalinised lignocaine has an advantage over its non-alkalinised form, due to a quicker onset, longer duration, and better quality of block. [5] Uncuffed ETT have traditionally been used in children due to their tracheal anatomy, and a fear of injury to the tracheal mucosa by the cuffed endotracheal tube (ETT). [15] However there is now a growing interest in the usage of high volume low pressure cuffs in children due to a reduced risk of aspiration and possibly due to a lower risk of accidental tracheal extubation. [16-18] Overall there is a paucity of studies in children comparing the incidence of postoperative LT morbidity after instillation of ETT cuff with lignocaine or saline. One of the studies using 0.5% alkalinised lignocaine was found to significantly reduce the incidence of post extubation (PEC) and post-operative sore throat (POST) as compared to saline and air in children. [18] We therefore want to investigate the efficacy of tracheal tube cuffs filled with saline or 0.5% lignocaine and 0.5% alkalinised lignocaine in reducing the incidence of laryngotracheal morbidity and maintaining the intracuff pressures in children.

MATERIAL AND METHODS

Study design and setting: We conducted a prospective randomized controlled trial at Department of Anaesthesia & Critical Care, Vardhman Mahavir Medical College & Safdarjung Hospital, Delhi after obtaining the institutional review board approval and a written, informed consent from the patients. We have followed CONSORT guidelines for optimal reporting of parallel group randomized trials. [19]

Inclusion & Exclusion Criteria: Children of either gender, between the age of 5 to 12 years with an American Society of Anaesthesiologists (ASA) grade 1-2, undergoing surgery of more than 60 minutes duration, were considered for inclusion in the study. Children having an active upper respiratory tract infection, hyper-reactive airway, any history of allergy to lignocaine, predicted difficult airway,

oropharyngeal or neck malformations and stridor or dysphonia and requirement of more than two attempts at endotracheal intubation, were excluded from the study. Other criterias for exclusion were requirement of airway surgery or more than two attempts at endotracheal intubation, treatment with medications such as steroids or intravenous lignocaine and use of nasogastric or orogastric tube. Primary objective was to compare the efficacy of intracuff 0.5% alkalinized lignocaine, 0.5% lignocaine and saline in reducing the incidence of postoperative sore throat and post extubation cough (PEC) in children undergoing elective surgery. The secondary objective was to compare the efficacy of intracuff 0.5% alkalinized lignocaine, 0.5% lignocaine and saline in maintaining intracuff pressures. Assuming the difference of POST (primary outcome) between 0.5% alkalinized lignocaine, 0.5% lignocaine and saline in adult patients undergoing GA as 12%, the minimum required sample size while considering 90% power of study and two sided alpha error as 5%, was calculated to be 38 patients for group. Therefore, total sample size was 120 (40 for each group).

Randomization: Patients were randomly allocated into one of the three groups- S, L, AL as shown in **Figure 1.** Randomization to each group was determined by the opening sealed opaque envelope containing either saline or test drugs. The test drug was prepared by a separate anaesthesiologist who did not take part in the study and the syringes were disguised with a paper wrap. All the test drugs were prepared in 10 ml syringes with a total volume of 10 ml. Composition of 0.5% lignocaine included 2.5 ml of 2% lignocaine and 7.5 ml of normal saline whereas 0.5% alkalinised lignocaine included addition of 2.5 ml of 2% lignocaine to 7.5 ml of normal saline followed by disposal of 0.5 ml of mixed solution and further addition of 0.5 ml of 7.5% sodium bicarbonate (NaHCO3). Randomization was double blind as both patients and the researchers were unblinded to the substance used.

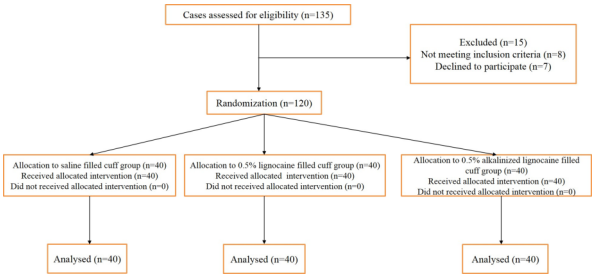

Figure 1:- Consort diagram showing random allocation to three different groups

Procedure: After induction with standard anaesthetic protocol, all patients were intubated with endotracheal tubes of appropriate sizes (according to the age of the patients), and the cuffs were inflated with required volumes of 0.9% saline, 0.5% lignocaine and 0.5% alkalinised lignocaine in groups S, L and AL respectively till a cuff pressure of 20-30 cm of water was reached, as determined by a cuff manometer.

Pre-operative period

The patients or their attendants were explained about the scoring system for laryngotracheal morbidity in their own language for ease of assessment in the postoperative period. All the patients were made to fast as per guidelines and received premedication with syrup Triclofos 50mg/kg body weight night before surgery. Patients were taken to the operation theatre and standard monitors were attached before induction of anaesthesia. Basal parameters such as heart rate (HR), blood pressure: Systolic, Diastolic and Mean (SBP, DBP, MAP), Oxygen saturation (SpO2) and Electrocardiography (ECG) were recorded.

Intraoperative period

Induction: The standard anaesthetic protocol consisted of an inhalational induction with 8% sevoflurane in 50% nitrous oxide and oxygen, followed by an intravenous (IV) access with a 24/22 gauge cannula. IV induction was done if the child allowed IV access, followed by pre-oxygenation with 100% oxygen for 3 minutes. Fentanyl 1.5- 2 mcg/ kg IV was administered. Propofol 1-2mg/kg IV was administered if required. After checking for manual ventilation of lungs, muscle relaxation was provided with vecuronium bromide 0.1 mg/kg IV. IPPV was provided with O2, N2O and Isoflurane for 3 mins, after which N2O and isoflurane was switched off, prior to intubation.

ETT Insertion: A direct laryngoscopy was performed using a laryngoscope with a curved blade. An appropriately sized cuffed Polyvinylchloride tracheal tube with a low pressure, high volume cuff which was fully deflated was orally inserted into the trachea. Size was calculated as Internal diameter (ID) = Age/4 +4 mm**.** Immediately after induction the cuff was slowly filled with the randomly allocated substance until an intracuff pressure (ICP) of 20cm of water was reached and a seal was ensured during manual ventilation with positive pressure. N2O and Isoflurane were switched on. Mechanical ventilation of the lungs were commenced with the ventilator set to deliver a tidal volume of 8ml/kg.

Parameters to be recorded during induction: The minimal occlusive volume, MOV (i.e the volume sufficient to establish a cuff pressure of 20cm of water and prevent air from leaking during positive pressure ventilation) will be noted. 2) HR, SBP, DBP, MAP, SpO2, End tidal carbon dioxide (ETCO2). 3) Peak airway pressure (Paw) and exhaled tidal volume (TVE) will be noted at 5 and 15 minutes after intubation.

Maintenance: The ETT was connected to the circle absorber and IPPV continued. Anaesthesia was given using O2, N2O, Isoflurane (FiO2: 0.3). Vecuronium bromide and Fentanyl were given whenever required and IV Paracetamol 15mg/kg was administered for supplemental analgesia. Injection ondansetron 0.15mg/kg was given 30 minutes before the end of surgery.

Parameters to be measure intraoperatively are: 1) Intracuff pressure every 15 minutes 2) HR, SBP, DBP, MAP, SpO2, ETCO2, TVE, Paw every 15 minutes after intubation and 5 minutes before extubation.

Reversal: Inhalational anaesthetic (isoflurane) was switched off 5 minutes prior to the end of surgery. At the end of surgery, neuromuscular blockade was reversed with IV neostigmine (0.05 mg/kg) and IV glycopyrrolate (0.01 mg/kg). All patients were given 100% oxygen during emergence from anaesthesia. ETT was removed after a thorough pharyngeal suctioning, when the patient was fully awake and responding to verbal commands.

Postoperative Period

Following parameters were measured during extubation – **(**a) HR, BP (SBP, DBP, MAP) and SpO2 recorded 5 minutes after extubation; **(**b) Post extubation cough (PEC) defined as patient coughing, when breathing regularly or irregularly with the ETT in place (Grade 0- No, Grade 1- +, Grade 2- ++); **(**c) Bucking, Laryngospasm, Bronchospasm, Stridor (Grade 0- Absent, Grade 1- Present); (d) Desaturation, Spo2 <90% (Grade 0- Absent, Grade 1- Present) ; (e) Blood staining on the device on removal (Grade 0- Absent, Grade 1- Present); (f) Tongue, lip or dental trauma (Grade 0- Absent, Grade 1- Present) ; (g) Time of spontaneous ventilation**;** (h) Smooth extubation - If PEC Grade is 0 or 1.

Laryngotracheal morbidity - Following parameters were assessed at 1, 8 and 24 hours post-operatively:- (a) Cough (Grade 0 = no cough, Grade 1 = cough<15s, Grade 2 = cough>15s); (b) Sore throat (Grading: Grade 0 = no sore throat, Grade 1 = mild (< cold), Grade 2 = moderate (=cold), Grade 3 severe (> cold); (c) Dysphonia (Grade 0 = no hoarseness, Grade 1 = mild (noticed by the patient), Grade 2= moderate (noticed at the time of interview) , Grade 3 = severe (aphonia); (d) Dysphagia (Grade 0= No dysphagia, Grade1= To solids, Grade 2= to liquid, Grade 3= on salivation) ; (e)Postoperative nausea and vomiting (PONV)- (Grade 0= no PONV, Grade 1= PONV +); (f) Pain- assessed by faces pain scale

Statistical Details: Categorical variables were presented in number and percentage (%) and continuous variables presented as mean + standard deviation (SD) and median. Normality of data was tested by Kolmogorov-smirnov test. If the normality was rejected, then non parametric test was used. Quantitative variables were compared using unpaired t-test/ Mann-Whitney test (when the data sets were not normally distributed) between the two groups. Qualitative variables were compared using Chi square test/ Fisher's exact test. A p value of < 0.05 was considered as statistically significant. The data was entered in MS Excel spreadsheet and analysis was done using latest version of Statistical Package for Social Sciences (SPSS) statistics version 26.

RESULTS

Demographic variables were comparable in all the three groups in terms of age, sex and anthropometric parameters (weight, height, body mass index) as shown in **Table 1**. The mean duration of surgery in the Groups

S, L and AL were 78, 76 and 79 minutes respectively and were comparable (p=0.68). The mean duration of anesthesia in the Group S was 108 minutes while in Group L and AL was 106.5 and 109.5 minutes respectively and were comparable (p=0.68). Majority of the patients were intubated with 6.5 mm ETT (28%, 35% and 31% in Group S, Group L and Group AL respectively). Intubation in the first attempt was observed in majority of patients (Group S = 85%, Group L = 82.5%, Group AL = 87.5%) but there was no difference among the groups. Intraoperative parameters like heart rate, mean arterial pressure, $ETCO_2$, SpO2, intracuff pressure, exhaled tidal volume, peak airway pressure were monitored and compared among all the groups with no clinically significant difference as shown in **Table 2**. The intracuff pressures were serially monitored at 5, 15, 30, 45, 60, 90 and 105 minutes following intubation and 5 minutes prior to extubation which were comparable across the groups and the difference was statistically insignificant (T5: p=0.307, T15: p=0.087, T30: p=0.984, T45: p=0.456, T60: p=0.534, T90: p=0.987, T105: p=0.984, TE (-5): p=0.095). At extubation the incidence of desaturation, blood staining of ETT on removal and tongue, lip or dental trauma showed no statistically significant difference among all the groups as shown in **Table 3**. Postoperatively patients were followed up at 1 hour, 8 hour and 24 hours as shown in **Table 4**. The incidence of smooth extubation was 85%, 77.5%, 20% in Group AL, L and S respectively. The incidence of smooth extubation was significantly more with alkalinized lignocaine as compared to lignocaine (p=0.001) and saline (p=0.001) and in lignocaine as compared to saline (p=0.001). The incidence of bucking, laryngospasm and bronchospasm was significantly less with alkalinized lignocaine as compared to saline (p=0.001) and in lignocaine as compared to saline (p=0.001). However it was comparable between alkalinized lignocaine and lignocaine (p=0.51). The incidence and severity of cough immediately after extubation was 75%, 17.5% and 0% in Group S, L and AL respectively. It was found that alkalinized lignocaine was significantly superior to lignocaine (p=0.001) and saline (p=0.001) and lignocaine was significantly better than compared to saline (p=0.001). The incidence and severity of cough and sore throat at 1 and 8 hours was significantly less with alkalinized lignocaine as compared to lignocaine (1 hour - p=0.001, 8 hours – p=0.002) and saline (1 hour - p=0.001, 8 hours – p=0.002) and in lignocaine as compared to saline (1 hour p=0.002, 8 hours p=0.003). The incidence and severity of cough and postoperative sore throat at 24 hours was significantly less in alkalinized lignocaine group as compared to saline (p=0.001) and in lignocaine as compared to saline (p=0.002). No difference was found between lignocaine and alkalinized lignocaine for cough (p=0.747) and sore throat (p=0.091). The incidence and severity of dysphonia at 1 hour was significantly less with alkalinized lignocaine as compared to lignocaine (p=0.001) and saline (p=0.001) and in lignocaine as compared to saline (p=0.001). The incidence and severity of dysphonia at 8 and 24 hours postoperatively was significantly less in alkalinized lignocaine group as compared to saline (8 hours - p=0.001, 24 hours- p=0.001) and in lignocaine as compared to saline (8 hours p=0.001, 24 hours p=0.001). However it was comparable between alkalinized lignocaine and lignocaine (8 hours - p=0.459, 24 hours – 0.970). In our study, there was a no statistically significant decrease in the incidence of dysphagia, PONV and pain at 1 hour, 8 hours and 24 hours following extubation.

Table 1:- Demographic profile of three groups

Characteristics	Groups			P value
	Group S(n=40)	Group L (n=40)	Group AL(n=40)	
Age in years (Mean ± SD)	8.60 ± 2.46	9.10 ± 2.20	8.45 ± 2.29	0.42
Gender Male Female	 21 (52.5%) 19 (42.5%)	 24 (60%) 16 (40%)	 17 (42.5%) 23 (57.5%)	0.29
Height in cms	123.02±9.79	124.69±7.88	121.52±9.55	0.30
Weight in kg	22.02±6.79	23.65±4.35	23.02±6.24	0.46
BMI in kg/mtr2	14.29±2.72	15.11±1.90	15.28±2.13	0.12
Duration of surgery	78.00±14.88	76.50±15.11	79.50±16.01	0.68
Size of endotracheal tube	6.51±0.52	6.51±0.43	6.52±0.45	0.99
Number of attempts of intubation One Two	 34 (85%) 6 (15%)	 33 (82.5%) 7 (17.5%)	 35 (87.5%) 5 (12.5%)	0.82
Duration of anesthesia	108.00±14.88	106.50±15.11	109.50±16.01	0.68
Time to spontaneous ventilation after reversal	5.77±0.91	5.60±0.78	5.40±0.70	0.66

Table 2:- Trends in intra-operative parameters observed among three groups

Characteristics	Time interval after induction	Groups			ANOVA F value	P value
		Group S(n=40)	Group L (n=40)	Group AL (n=40)		
Heart rate	T0	102.98 ± 12.25	94.65 ± 9.38	82.29 ± 5.35	57.422	0.10
	T5	105.14 ± 10.92	111.45 ± 9.79	95.50 ± 7.64	31.784	0.21
	T15	94.25 ± 14.91	69.03 ± 7.09	69.46 ± 7.10	85.056	0.12
	T30	81.11 ± 11.38	68.20 ± 11.19	67.40 ± 5.45	28.541	0.31
	T45	77.50 ± 9.71	66.65 ± 10.23	67.00 ± 5.82	22.110	0.12
	T60	75.39 ± 9.14	69.10 ± 8.38	66.13 ± 5.38	16.998	0.41
	T90	73.25 ± 9.84	68.48 ± 8.52	66.17 ± 4.77	9.472	0.10
	T105	72.39 ± 9.92	67.48 ± 9.94	66.17 ± 4.11	7.018	0.12
	TE (-5)	75.00 ± 12.65	70.58 ± 10.03	68.38 ± 5.89	5.364	0.76
	TE (+5)	87.91 ± 19.30	102.08 ± 13.21	94.27 ± 7.52	10.658	0.55
Mean arterial pressure	T0	69.16 ± 7.76	64.73 ± 5.12	67.25 ± 4.92	5.617	0.15
	T5	68.39 ± 4.91	64.38 ± 5.55	65.56 ± 5.26	6.619	0.11
	T15	68.02 ± 4.87	61.40 ± 7.73	65.46 ± 4.22	14.329	0.13
	T30	68.55 ± 3.45	62.90 ± 6.74	65.35 ± 5.39	11.945	0.77
	T45	68.55 ± 3.68	64.33 ± 6.23	65.88 ± 4.26	8.455	0.15
	T60	69.32 ± 4.87	63.73 ± 5.50	64.94 ± 3.25	17.848	0.35
	T90	68.52 ± 5.92	65.33 ± 4.99	66.27 ± 2.40	5.408	0.15
	T105	67.41 ± 4.39	66.25 ± 4.08	65.38 ± 4.35	2.600	0.08
	TE (-5)	68.07 ± 4.72	68.95 ± 4.29	66.48 ± 4.41	3.475	0.90
	TE (+5)	69.66 ± 6.24	72.60 ± 4.04	67.02 ± 3.14	15.796	0.46
Oxygen saturation (SpO2)	T0	99.61± 0.58	99.08 ±0 .73	99.19 ±0.96	5.716	0.21
	T5	99.59 ± 0.66	98.28 ± 1.04	99.23 ± 0.83	26.623	0.10
	T15	99.59 ± 0.58	99.08 ±0 .99	98.81 ± 1.12	8.151	0.11
	T30	99.61 ± 0.62	99.13 ±0.91	98.98 ± 0.86	7.647	0.35
	T45	99.59 ± 0 .62	99.25 ± 142.35	99.40 ± 0.74	1.078	0.34
	T60	99.32 ± 0.80	98.63 ± 1.23	98.96 ± 0.80	5.573	0.91
	T90	99.36 ± 0.718	98.70 ± 1.32	98.75 ± 0.89	6.033	0.09
	T105	99.30 ± 0 .82	98.90 ± 1.08	98.90 ± 0.69	3.078	0.54
	TE (-5)	99.16 ± 0.99	99.28 ± 1.05	98.98 ± 0.84	1.113	0.99
	TE (+5)	98.73 ± 1.21	98.00 ± 1.60	99.44 ± 0.80	15.135	0.68

End tidal carbon dioxide (ETCO2)	T0	40.84 ± 15.99	36.65 ± 1.25	36.08 ± 1.22	3.486	0.89
	T5	36.39 ± 1.15	36.13 ± 1.16	36.35 ± 1.10	0.658	0.52
	T15	36.59 ± 1.17	35.55 ± 0.93	35.90 ± 1.26	9.236	0.56
	T30	36.64 ± 1.37	35.83 ± 0.93	35.33 ± 1.59	10.941	0.22
	T45	36.73 ± 1.28	35.90 ± 1.08	35.90 ± 0.99	7.997	0.98
	T60	36.82 ± 1.35	36.13 ± 1.09	35.81 ± 1.21	7.973	0.16
	T90	36.80 ± 1.27	36.45 ± 1.22	35.77 ± 1.15	8.541	0.97
	T105	36.70 ± 1.30	36.10 ± 1.32	35.92 ± 1.01	5.235	0.89
	TE (-5)	36.50 ± 1.05	41.28 ± 31.29	36.17 ± 1.17	1.155	0.52
Intra-cuff pressures	T5	15.00 ± 2.40	16.60 ± 9.65	16.54 ± 0.74	1.193	0.31
	T15	15.48 ± 2.04	15.38 ± 1.72	17.25 ± 0.86	19.889	0.09
	T30	15.55 ± 2.04	15.35 ± 1.81	17.56 ± 0.87	25.815	0.98
	T45	15.64 ± 2.00	15.33 ± 1.87	17.83± 0.93	31.369	0.46
	T60	15.68 ± 2.06	15.48 ± 1.74	18.04 ± 0.90	35.457	0.53
	T90	15.77 ± 2.03	15.58 ± 1.80	18.17 ± 1.04	34.587	0.99
	T105	16.00 ± 1.84	15.63 ± 1.64	18.40 ± 1.14	42.344	0.98
	TE (-5)	16.07 ± 1.84	15.60 ± 1.58	18.65 ± 1.04	53.682	0.10
Peak airway pressure (Paw)	T5	15.00 ± 2.40	16.60 ± 9.65	16.54 ± 0.74	1.193	0.31
	T15	15.48 ± 2.04	15.38 ± 1.72	17.25 ± 0.86	19.889	0.09
	T30	15.55 ± 2.04	15.35 ± 1.81	17.56 ±0 .87	25.815	0.98
	T45	15.64 ± 2.00	15.33 ± 1.87	17.83 ± 0.93	31.369	0.46
	T60	15.68 ± 2.06	15.48 ± 1.74	18.04 ± 0.90	35.457	0.83
	T90	15.77 ± 2.03	15.58 ± 1.80	18.17± 1.04	34.587	0.75
	T105	16.00 ± 1.84	15.63 ± 1.64	18.40 ± 1.14	42.344	0.98
	TE (-5)	16.07 ± 1.84	15.60 ± 1.58	18.65 ± 1.04	53.682	0.55
Exhaled tidal volume (Vte)	T5	158.43 ± 63.66	150.70 ± 49.55	190.83 ± 70.93	5.224	0.77
	T15	161.02 ± 59.20	154.13 ± 51.22	194.81 ± 71.28	5.637	0.99
	T30	161.05 ± 58.88	151.00 ± 48.15	193.98 ± 71.15	6.156	0.46
	T45	157.93 ± 55.45	150.65 ± 46.29	196.48 ± 68.99	8.076	0.35
	T60	160.39 ± 58.25	150.65 ± 46.49	198.08 ± 70.58	7.880	0.46
	T90	162.98 ± 63.16	150.40 ± 47.53	200.17 ± 72.39	7.683	0.87
	T105	161.50 ± 55.80	148.40 ± 45.19	200.83 ± 72.70	9.360	0.99
	TE (-5)	160.09 ± 57.02	144.40 ± 50.72	201.40 ± 73.34	10.183	0.93

Table 3:- Parameters noted at extubation among three groups

Characteristics	Groups			P value
	Group S (n=40)	Group L (n=40)	Group AL (n=40)	
Post extubation cough				
Grade 0	0 (0%)	1 (2.5%)	32 (80%)	0.001
Grade 1	10 (25%)	32 (80%)	8 (20%)	
Grade 2	30 (75%)	7 (17.5%)	0 (0%)	
Bucking, Laryngospasm, Bronchospasm				
Grade 0	31 (77.5%)	9 (22.5%)	5 (12.5%)	0.001
Grade 1	9 (22.5%)	31 (77.5%)	35 (87.5%)	
Desaturation (SpO2 < 90%)				
Present	5 (12.5%)	4 (10%)	8 (20%)	0.41
Absent	35 (87.5%)	36 (90%)	32 (80%)	
Blood staining of ETT on Removal				
Grade 1	8 (20%)	6 (15%)	6 (15%)	0.78
Grade 0	32 (80%)	34 (85%)	34 (85%)	
Tongue, lip or dental trauma				
Grade 1	9 (22.5%)	3 (7.5%)	9 (22.5%)	0.12
Grade 0	31 (77.5%)	37 (92.5%)	31 (77.55)	
Smooth extubation				
Grade 1	8 (20%)	31 (77.55)	34 (85%)	0.001
Grade 0	32 (80%)	9 (22.55)	6 (15%)	

Table 4:- Laryngotracheal morbidities observed among three groups

Characteristics	Groups									P value
	Group S (n=40)			Group L (n=40)			Group AL (n=40)			
	T 1	T8	T24	T1	T8	T24	T1	T8	T24	
Cough										0.001
Grade 0	0 (0%)	0 (0%)	11 (27.5%)	6 (15%)	12 (30%)	34 (85%)	36 (90%)	37 (92.5%)	35 (87.5%)	
Grade 1	8 (20%)	10 (25%)	29 (72.5%)	34 (85%)	28 (70%)	6 (15%)	4 (10%)	3 (7.5%)	5 (12.5%)	
Grade 2	32 (80%)	30 (75%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Sore throat										0.001
Grade 0	0 (0%)	0 (0%)	7 (17.5%)	8 (20%)	6 (15%)	36 (90%)	34 (85%)	35 (87.5%)	40 (100%)	
Grade 1	0 (0%)	10 (25%)	33 (82.5%)	32 (80%)	34 (85%)	4 (10%)	6 (15%)	5 (12.5%)	0 (0%)	
Grade 2	13 (32.5%)	30 (75%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Grade 3	27 (67.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Dysphonia										0.001
Grade 0	0 (0%)	6 (15%)	9 (22.5%)	8 (20%)	35 (87.5%)	35 (89.7%)	37(92.5%)	37 (92.5%)	36 (90%)	
Grade 1	4 (10%)	34 (85%)	31 (77.5%)	32 (80%)	5 (12.5%)	4 (10.3%)	3 (7.5%)	3 (7.5%)	4 (10%)	
Grade 2	36 (90%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

Post-operative nausea and vomiting Grade 0 Grade 1	34 (85%) 6 (15%)	34 (85%) 6 (15%)	40 (100%) 0 (0%)	34 (85%) 6 (15%)	34 (85%) 6 (15%)	40 (100%) 0 (0%)	34 (85%) 6 (15%)	34 (85%) 6 (15%)	40 (100%) 0 (0%)	1.00
Mean pain score (faces pain scale)	0.92 ± 1.55	0.35 ± 0.48	0.15 ± 0.36	0.98 ± 1.67	0.35 ± 0.48	0.15 ± 0.36	0.98 ± 1.51	0.35 ± 0.48	0.18 ± 0.38	0.98

DISCUSSION

We undertook a double blind randomized control study to compare the efficacy of intra cuff 0.5% alkalinized lignocaine, 0.5% lignocaine and saline on endotracheal tube induced laryngotracheal morbidity in children. Endotracheal intubation remains the gold standard procedure for airway management with an ability to achieve all the goals of airway management such as providing a secure airway, optimal mechanical ventilation and protection of airway from risk of gastric content aspiration during general anesthesia. [20] The high pressure – low volume cuffs were introduced in 1960s with the aim of preventing gastric aspiration and to ensure minimal leak during positive pressure ventilation. However it was observed that serious complications were encountered with the use of high pressure, low volume cuff endotracheal tube (ETT) particularly after long-term intubation. When the intracuff pressure was more than 30 mmHg, it abolished mucosal blood flow, resulting in ischemia and subsequently tracheal stenosis or tracheomalacia. This effect was more pronounced in children due to lower mucosal perfusion pressures. [21] This led to the advent of high volume low pressure (HVLP) cuff which comprises of a thin compliant wall which when inflated, adapts and conforms easily to the irregular borders of the tracheal wall with an intracuff pressure closely correlating with tracheal mucosal pressure. [22] Though microaspiration can occur at pressures upto 60 cm H_2O, it was observed that an intracuff pressure greater than 34 cm H_2O results in decreased perfusion to the trachea. Hence cuff pressure is usually kept 15-20 mm Hg (20-30 cm H_2O) was agreed upon to be a reasonable limit of cuff pressure in adults when using HVLP polyvinyl chloride cuffs. [23] With the increasing use of cuffed ETTs in children less than 8 years of age, a better understanding of technical difficulties and adverse effects is of paramount importance. The use of cuffed ETTs in children confer advantages such as improved monitoring of end-tidal gas, decreased risk for aspiration and ability to achieve high inflation pressures with low fresh gas flows. [24] However it is postulated to be associated with pronounced laryngotracheal complications related to cuff pressures, as infants and children have a relatively small larynx, trachea and are more prone to airway edema. [20] Placing an ETT with a small internal diameter may also limit suctioning capability. [24] Nitrous oxide used for general anesthesia may diffuse into the air-filled endotracheal cuff resulting in an increase in the cuff pressure, leading to over- inflation of the cuff with resultant tracheal damage. [25] This may result in an increased incidence of post extubation laryngotracheal morbidity which may manifest as cough, pharyngeal dryness, sore throat, dysphagia, odynophagia or dysphonia following extubation. [21] Stanley TH et al, observed in their study that intra-operative diffusion of nitrous oxide into air-filled spaces increases the volume of the ETT cuff by 9 – 38% within the first 30 minutes of anesthesia. Excessive endotracheal tube cuff pressure was observed to impair tracheal mucosal perfusion and cause tracheal damage and sore throat. [25] Combes X et al, used intra cuff instillation of saline in ETT cuff in adult patients in 2001 and observed that the cuff pressure remained stable in the group with ETT cuff filled with saline and the incidence of sore throat and tracheal lesions was significantly lower in the saline group both in the post anesthesia care unit and 24 h after extubation. [26] This suggested that an excessive increase in endotracheal tube cuff pressure during balanced anesthesia due to nitrous oxide diffusion into this closed gas space, caused sore throat related to tracheal mucosal erosion and this can be attenuated by filling the cuff with saline. [26] Subsequently similar observations of benefits of intracuff saline over air was made by other studies. [27, 28] Sconzo JM et al, in their in vitro study observed that lidocaine, when administered as a cuff inflation medium, may protect the tracheal mucosa through its continuous topical anesthetic effect, thus preventing diffusion of nitrous oxide into the cuff. [29] This was further supported by studies done by Dollo et al and Navarro et al. [14, 30] Estebe JP et al, observed that alkalinisation of lidocaine had an advantage over its non-alkalinized variety due to quicker onset of action, longer duration and better quality of block and reported that alkalinized lidocaine diffused through the membrane of the cuff 60 times more than non-alkalinized lidocaine in a 6-h period facilitating instillation of lower dose with minimal systemic effects. [31] This was followed by several randomized controlled trials (RCTs) which aimed at investigating the prophylactic efficacy of intracuff lidocaine on the post-intubation-related emergence phenomenon in adults, providing inconclusive results. [28,30-32]However a systematic review to assess the effect of intracuff lignocaine on post-operative sore throat and emergence phenomenon in adult patients, reported that both alkalinized and non-alkalinized lidocaine in the subgroup analyses showed significant benefits in emergence phenomena prevention when compared with the control and no complications related to lidocaine overdose or endotracheal cuff rupture was observed. [33] The extrapolation of such results to pediatric population may not be ideal due to the peculiar airway anatomy of children and the technical difficulties during intubation with a cuffed ETT. Well conducted studies are required before definite recommendations on the role of intra cuff lidocaine can be made in children. However, data available in pediatric population is scarce. Ahmady SM et al, did a randomized controlled (RCT) study in 2013 to investigate the efficacy of intra-cuff alkalinized lidocaine in the prevention of the endotracheal tube (ETT) induced emergence phenomena in 50 children. [34] The study included children, aged 6 – 12 years undergoing elective dental surgery. It was observed that there was a significant reduction in the incidence ($p=0.005$) and severity ($p= 0.014$) of cough at extubation and in the post anesthesia care unit (incidence of cough: $p=0.048$ & severity of cough $p=0.014$) in the group whose cuff was filled with alkalinized lignocaine in comparison to normal saline group. Alkalinized lignocaine group also had reduction in incidence of sore throat, improved ETT tolerance and smooth extubation, but had prolonged time to spontaneous ventilation before extubation. [34] This was supported by another RCT by Soares SM et al, in their randomized trial to study the effect of tracheal tube cuffs filled with air, saline or alkalinized lidocaine on hemodynamic changes during tracheal extubation and postoperative laryngotracheal morbidity in children observed that the mean (SD) increases in heart rate after tracheal extubation compared with those before extubation was significantly lower in 1% alkalinized lidocaine group ($p < 0.001$) in comparison to air, saline and 0.5% alkalinized lidocaine group. The incidence of sore throat was significantly lower in alkalinized lidocaine group, ($p = 0.015$) suggesting that filling the tracheal tube cuff with alkalinized lidocaine reduced the hemodynamic response to tracheal extubation and postoperative laryngotracheal morbidity in children. [35] However both the studies had variations in their methodology and target population making generalizability of study results difficult. In our double blind randomized control study, the primary objective was to compare the efficacy of intra cuff 0.5% alkalinized lignocaine, 0.5% lignocaine and saline on endotracheal tube induced laryngotracheal morbidity in children.

In our study we observed that the incidence of smooth extubation, bucking, laryngospasm and bronchospasm in the post-extubation period was significantly lower in lignocaine and alkalinized lignocaine group with greater benefit in the latter. Laboratory studies have observed that manipulation of ETT cuff at the time of extubation may act as an irritant and cause the stimulation of the rapidly adapting stretch receptors (RAR) in the tracheal mucosa. This may result in stimulation of the receptors resulting in release of various inflammatory mediators such as substance P, calcitonin gene-related peptide and neurokinin A which are associated with mucosal vasodilatation, plasma exudation, airway mucus secretion and bronchoconstriction. [36] The above process has been implicated as reason for occurrence of cough, bucking, laryngospasm and bronchospasm during extubation. Dollo et al, in their study observed that the diffusion of uncharged base form of lignocaine across the hydrophobic polyvinyl chloride (PVC) wall of the ETT cuff resulted in blocking of these cough receptors. [14] This may be attributed as one of the potential reasons for a significant reduction in the occurrence of the adverse events at the time of extubation with the use of ETT cuff filled with lignocaine or alkalinized lignocaine.

Our findings were substantiated by another randomized study of 75 patients with a history of chronic smoking or recently treated upper respiratory tract infections who were assigned into three groups based on the type of agent used for endotracheal tube cuff inflation. It was observed that group with ETT cuff inflated with buffered lidocaine

produced significantly greater incidence of smooth extubation even in patients with hyperactive airways in comparison to saline and lignocaine group. [37] Navarro et al, in their study as well observed that, ETT cuffs filled with alkalinized lidocaine prevented the occurrence of high cuff pressures during N_2O anesthesia and reduced ET discomfort. The authors concluded that alkalinized lidocaine-filled ET cuffs may be safer than conventional air- filled ET cuffs. [30] The above findings are further strengthened by findings of systematic review of nineteen trials, which comprised 1566 patients which showed a decreased incidence of agitation during extubation with use of intra cuff lignocaine. [33]

In our study, we have shown a significant reduction in the incidence and severity of post extubation cough, sore throat, dysphonia, cough at 1, 8 and 24 hours in both lignocaine and alkalinized lignocaine group in comparison to saline group (p= 0.0001). In addition, there was greater statistically significant reduction in the post extubation cough, sore throat, dysphonia and cough at 1, 8 and 24 hours in the alkalinized lignocaine group in comparison to lignocaine group (p=0.0001).

Studies by Shroff et al and Rizvanović et al on adult patients also suggested similar benefits of alkalinized lignocaine. [38, 39] The findings of our study was further substantiated by a systematic review of nineteen trials and 1566 adult patients which observed that the incidence of early- and late-phase postoperative sore throat (POST), coughing, agitation, hoarseness, and dysphonia decreased significantly in lidocaine groups, with relative risk of 0.46, 0.41, 0.43, 0.37, 0.43 and 0.19, respectively, when compared with the control groups. Both alkalinized and non-alkalinized lidocaine in the subgroup analyses showed significant benefits in emergence phenomena prevention when compared with the control. [33] Navarro et al, in their study of 50 adult patients observed that ET cuffs filled with alkalinized lidocaine resulted in reduction of ET discomfort and postoperative sore throat incidence. They attributed the benefit of alkalinized lignocaine akin to that of the intracuff instillation of saline for prevention of increase in cuff pressure secondary to the diffusion of nitrous oxide into the cuff of the endotracheal tube intraoperatively as observed in study by Combes X et al. [26, 30] However the variations in the intraoperative cough pressure in the present study was not statistically insignificant to support this hypothesis.

An alternative explanation for the efficacy of the lignocaine and alkalinized lignocaine may be possibly due to diffusion of the drugs across the cuff membrane. In vitro studies by Estebe et al and Sconzo et al, demonstrated that measurable amounts of local anesthetic used to fill tracheal tube cuffs diffused through the cuff membranes in a dose- and time-dependent fashion. [29,31] Further the greater significant reduction in the outcome parameters with alkalinized lignocaine further substantiate the fact that diffusion of drug across the cuff membrane as the reason for decreased PEC, sore throat, dysphonia, cough at 1, 8 and 24 hours rather than prevention of increase in cuff pressure by diffusion of N2O during anesthesia. This fact is supported by in vitro studies by Estebe et al, who had observed greater diffusion with alkalinized lignocaine. [40] Similar observations was made by Ahmady, et al who had showed that use of intra-cuff alkalinized lidocaine reduced the incidence of cough, sore throat, improved ETT tolerance and inducing smooth extubation in pediatric patients who were scheduled for elective dental surgery under N_2O free general anesthesia. [34] The above findings were further substantiated by observations of a study on Indian patients demonstrating a lower incidence of sore throat in lignocaine group as compared to air group. [41] Study by Gaur et al, and two other studies on adult Indian patients also revealed similar results. [42] In another randomized study from India of 75 patients assigned to 3 groups (Air, Normal saline & Alkalinized lignocaine) on patients with history of chronic smoking or recently treated upper respiratory tract infections, it was observed that injecting buffered lidocaine into the endotracheal tube cuff produced smooth extubation even in patients with hyperactive airways. The authors attributed the effect the to blocking of the cough receptors in the tracheal mucosa by the increased diffusion of uncharged base form of the drug across the hydrophobic polyvinyl chloride wall of the cuff as observed in our study on pediatric population. [43] However, Soares et al, in their study on pediatric patients observed that though there was a reduction in post operative sore throat, post extubation dysphonia and cough did not differ significantly in alkalinized lignocaine group. The authors explained the discrepancy of their results may be due to the low serum concentrations of lignocaine. [35] One of the reasons for the postoperative sore throat could be the result of activation of tracheal nociceptors and the continuous application of local anesthetic to the tracheal mucosa may reduce its occurrence. The benefits observed with lignocaine and alkalinized lignocaine may be due to relatively low lidocaine concentrations which are able to block different sensory tracheal receptors and suppress their action potentials. [32] Furthermore, the reduction in the incidence of sore throat at 8 hour and 24 hour following extubation might be related to its anti- inflammatory action of intracuff lignocaine which had diffused across the cuff membrane. [29,44] The delayed analgesic and anti-inflammatory effects of lignocaine may be through its actions on potassium and calcium channels and on G protein- coupled receptors [45] and studies have observed that the effects can persist for days to weeks even after a decrease in its plasma level. [46] In our study it was found that there was a reduction in incidence and severity of dysphonia was significantly lower in both lignocaine and alkalinized lignocaine in comparison to the saline group with greater reduction in latter. The lack of statistical difference in number of intubation attempts, duration of surgery and anesthesia, variations in intracuff pressure intra-operatively made us postulate that prevention of bucking and laryngospasm and facilitating a smooth extubation in alkalinized lignocaine group could result in reduction of trauma to the vocal cords and upper airway. This may explain the reduction in incidence and severity of dysphonia in our study. Similar observations were made by systematic reviews in adult patients. [47] In our study, it was observed that the incidence and severity of dysphagia, post operative nausea, vomiting and pain did not differ significantly amongst the groups. Estebe et al, reported that alkalinized lidocaine diffused through the membrane of the cuff 60 times more than non-alkalinized lidocaine in a 6-h period enabling a low dose lidocaine (40 mg) to offer adequate protection after alkalinization . Plasma levels of lidocaine levels have been observed to vary with different routes of administration. With intravenous lidocaine plasma levels may reach upto 2 to 3 μg/mL [48, 49] topical application results in plasma levels from 0.43 to 1.5 μg/mL [50], and plasma concentrations with intra cuff alkalinized lidocaine were below 0.08μg/mL. [14, 31] This indicates that intracuff alkalinized lidocaine inflation resulted in a local effect, rather than a systemic one. This lack of systemic benefit with intracuff instillation of alkalinized lignocaine may explain the lack of benefit in incidence and severity of dysphagia, post-operative nausea, vomiting and pain amongst the groups. This study is only one of the few studies conducted on pediatric population addressing the impact of intracuff instillation of the saline vs lignocaine vs alkalinized lignocaine. It is a randomized double blinded study aimed at eliminating any confounding bias that would impact the outcome parameters. The homogeneity of the characteristics of population across the groups eliminate the possibility of confounders, adding greater value to the results of the study. The inclusion of pediatric population across a wide age group undergoing variety of surgeries under general anesthesia would make the results of the study generalizable. The results of the study will help in substantiating the available evidence on the benefits of intra cuff alkalinized lignocaine, particularly in pediatric population and may help in providing better patient care.

Our study has some limitations. Firstly, use of nitrous oxide was not excluded, as it may diffuse into the tracheal tube cuff and may increase cuff pressure, an important risk factor for laryngotracheal morbidity. However this limitation was addressed as the number of patients who received nitrous oxide was similar in all four groups and the tracheal tube cuff pressures were measured periodically to maintain a value between 20-30 cmH_2O. Secondly, sevoflurane, a commonly used inhaled anesthetic was not administered and its impact on cuff pressure may influence the outcome of the study. Finally the cuff pressures were measured manually though measures were taken to standardize the measurement.

It can be concluded that intra cuff instillation of alkalinized lignocaine resulted in an increased incidence of smooth extubation in comparison to lignocaine and saline, with lignocaine being significantly better than saline. It was noted that intra cuff instillation of alkalinized lignocaine was significantly better than lignocaine which was significantly better than saline in terms of reduction in the incidence of post extubation cough, cough and POST at 1 and 8 hours and dysphonia at 1 hour after extubation. Alkalinized lignocaine and lignocaine were significantly better than saline in the reduction of bronchospasm, laryngospasm and bucking, cough and POST at 24 hours, post-operative sore throat at 24 hours and dysphonia at 8 and 24 hours after extubation but no difference was found between Group L and AL. Based on the observations of our study, we would like to recommend the use of intra cuff instillation of alkalinized lignocaine for cuffed ETT in children

aged 5 – 12 years for decreasing the incidence of laryngotracheal comorbidities.

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