Original Article

Effect of single-dose intravenous lignocaine versus fentanyl on neuromuscular recovery time after general anesthesia in elective pediatric surgery: A randomized controlled pilot study

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Abstract

Background and Aims: Intravenous (IV) lignocaine is often used to prevent the airway response to extubation, especially in children to prevent respiratory adverse events. It is known to prolong the duration of action of neuromuscular blocking drugs, but data in children are limited. The primary objective of this study was to compare neuromuscular recovery time with IV lignocaine versus fentanyl, in pediatric patients undergoing elective surgery under general anesthesia (GA). Secondary objectives included the comparison of clinical parameters and respiratory complications.

Material and Methods: A randomized double-blind pilot study was conducted in 42 children aged 2–8 years undergoing GA with neuromuscular blockade, who received either 1.5 mg/kg of lignocaine or 0.5 mcg/kg of fentanyl IV, just prior to giving reversal at a train of four (TOF) count of 2–3. Time to achieve a TOF ratio of 0.9 and extubation and hemodynamic and respiratory parameters were noted. Incidences of coughing, bucking, laryngospasm, etc., were also noted. P value < 0.05 was considered significant.

Results: Demographic and operative data were similar. Time from reversal to TOF ratio of 0.9 was similar with both lignocaine (6.79 ± 3.03 mins) and fentanyl (6.79 ± 3.31 mins), $P = 0.99$. Time to extubation was also similar in both groups (8.14 ± 3.31 vs 9.19 ± 2.89 min), $P = 0.28$. Bucking incidence was higher with fentanyl (23.8%) vs lignocaine (9.5%), $P = 0.41$.

Conclusions: Single-dose IV lignocaine administered before reversal did not prolong neuromuscular recovery time compared to fentanyl, with a similar (low) incidence of respiratory events in pediatric patients.

Keywords: Airway, anesthesia recovery, fentanyl, lignocaine, neuromuscular monitoring, peri operative complications

Introduction

More than 40% of patients who undergo surgery under general anesthesia (GA), experience coughing during extubation.[1] Any event of persistent coughing, or breath holding leading to partial or complete airway obstruction and subsequent desaturation, is defined as a respiratory adverse event. Although a protective reflex, continuous coughing increases the reactivity of children's airways, making them prone to complications like atelectasis, laryngospasm, and hypoxemia.[2] Laryngospasm is a dreaded complication in the pediatric population. Among the various modalities studied extensively, lignocaine has been found to be a safe and effective method for the prevention of coughing and airway response to extubation and hence preventing laryngospasm and other perioperative respiratory adverse events (PRAE).[3-5]

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Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_460_23

How to cite this article: Dhar M, Sharma R, Payal YS, Gupta V, Rawat J, Sogal S. Effect of single-dose intravenous lignocaine versus fentanyl on neuromuscular recovery time after general anesthesia in elective pediatric surgery: A randomized controlled pilot study. J Anaesthesiol Clin Pharmacol 2025;41:73-8.

Submitted: 19-Oct-2023 **Revised:** 09-Dec-2023
Accepted: 20-Feb-2024 **Published:** 23-May-2024

Some literature suggests that local anesthetic drugs may prolong the duration of action of neuromuscular blocking drugs.[6-9] Residual muscle weakness is a potential cause of respiratory insufficiency and related complications in the postanesthesia care unit (PACU). Train-of-four (TOF) ratios <0.9 have been found to be associated with impairment of pharyngeal coordination, force of contraction, and increased risk of aspiration, which may lead to hypoxia and other postoperative respiratory complications.[10]

The use of neuromuscular monitoring has greatly reduced the risks associated with the use of intermediate to long-acting drugs. Yet, its application is still underutilized in most setups, with more reliance on clinical signs for assessing the adequacy of neuromuscular reversal for extubation.[11] In the hands of even a trained anesthesiologist, these clinical signs are not very reliable especially in the pediatric population. More so, data on effect of IV lignocaine on neuromuscular recovery are limited or lacking in the children undergoing elective surgery.

The main aim of the study was to establish safety of IV lignocaine in children in terms of its potential effect on neuromuscular recovery, so that its numerous perioperative uses including for prevention of PRAE as well as for multimodal analgesia may be assessed in future studies as is being done in adults. We hypothesized that a single dose of IV lignocaine given just before giving reversal may prolong the neuromuscular recovery time compared to giving IV fentanyl (as control) in pediatric patients undergoing elective surgery under GA. For the study, the statistical hypothesis was that lignocaine is not worse than fentanyl in terms of time to neuromuscular recovery. Fentanyl was chosen as a control with the assumption that it does not have any direct effect on neuromuscular junction and would be a more ethical alternative to giving only a placebo for the purpose of decreasing the response to extubation. The primary objective of the study was to compare the recovery times after giving IV lignocaine just prior to reversal versus giving fentanyl. The secondary objectives of the study were to compare the incidence of complications, i.e., cough, bronchospasm, laryngospasm, hypoxemia, etc., between the two groups, and to compare the hemodynamic and respiratory clinical parameters at the time of extubation of the trachea.

Material and Methods

A randomized controlled double-blind pilot study was conducted on pediatric patients undergoing elective surgery under GA with neuromuscular blockade. After approval from the Institutional Ethical Committee AIIMS/IEC/22/270 dated 27.05.2022, the trial was registered with the Clinical Trial Registry of India (CTRI/2022/06/043111). The manuscript was prepared following CONSORT guidelines for randomized trials. Patients meeting the inclusion criteria were enrolled in this study, after obtaining written informed consent from the parent/guardian. Inclusion and exclusion criteria: Patients aged 2–8 years of both genders with American Society of Anesthesiology physical status I and II undergoing surgery under GA with neuromuscular blockade were recruited for the study. Patients with a known allergy to amide local anesthetics, with a known seizure disorder, with a known or expected difficult airway, patients with renal, hepatic, or muscular disorders, and patients taking drugs affecting neuromuscular function were excluded from the study. The enrolled patients were randomly allocated into two groups. Lignocaine group (LG) and fentanyl group (FG).

This was a double-blind study. The physician administering the study drugs and the outcome assessor (a different physician) were blinded. Randomization was done by serially numbered, sealed opaque envelopes concealing the randomization group as determined by computer-generated random numbers. A nurse not involved in the study opened the envelope and prepared the drug in a 5 ml syringe diluted till either 3 ml or 5 ml based on weight of the child. The syringe was labelled by a code to hide the group allocation. Preoperative evaluation and nil per oral instructions were standardized for all patients. On the day of surgery, patients were premedicated with oral midazolam 0.5 mg/kg 30–40 min before taking into the operation theater (OT). On arrival in the OT, noninvasive blood pressure, pulse oximetry, electrocardiography, and neuro-muscular monitors were applied. Neuromuscular monitoring was done at the adductor pollicis (Mindray A7 anesthesia workstation, Shenzhen Mindray Bio-medical Electronics Co. Ltd). The accelerometry transducer was attached to the distal interphalangeal joint of the thumb. The two stimulating electrodes were put on the volar medial side of the forearm over the ulnar nerve just proximal to the wrist crease [Figure 1]. Baseline hemodynamic parameters were noted. In patients with an IV line *in situ*, induction of anesthesia was done with IV propofol 2 mg/kg and fentanyl 1 mcg/kg. In children with no IV access, inhalational induction was done with 50% oxygen and 8% sevoflurane following, which the IV line was secured and then given IV fentanyl. After calibration of the neuro-muscular monitor, atracurium 0.5 mg/kg was given to facilitate the securing of the airway with an appropriate-sized endotracheal tube (ETT). In all the patients, anesthesia was maintained with sevoflurane with oxygen and air to achieve a minimum alveolar concentration of 1. Lungs were mechanically ventilated to normocarbia as monitored by capnography. Neuromuscular monitoring was used to guide atracurium dosing to maintain a TOF count of 0–1.

On conclusion of surgery, after switching off the sevoflurane, either IV Lignocaine 1.5 mg/kg (in the group LG) or Fentanyl 0.5 mcg/kg (in the group FG) was given just before giving reversal (neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg at a TOF count of 2–3).[12-14] TOF was monitored every 20 s at this time till a TOF ratio of 0.9 was attained. Extubation criteria were a TOF ratio of 0.9 or more along with clinical adequacy of extubation: eye-opening (to calling out name/ spontaneous), strong hand grip/or moving or lifting all limbs, generating adequate tidal volume (6–8 ml/kg), regular breathing, and adequate arterial oxygenation (SpO2 > 95% on 40% fiO_2). Hemodynamics parameters were noted at the time of giving reversal, at extubation, and 5 min postextubation.

Patients were transferred to the PACU and supplemental oxygen was given by face mask (4–6 L/min) if required. Peripheral oxygen saturation (SpO2) was continually measured in the PACU. Any adverse respiratory events (defined as SpO2 < 92% or airway obstruction requiring intervention, i.e., oropharyngeal airway, neck extension, chin lift, or jaw thrust) occurring in the PACU were recorded and managed.

The primary outcome of the study was measured as time from giving the reversal drug to achieving a TOF ratio of 0.9. Time from giving reversal to extubating the trachea was also noted. Any incidence of coughing, bucking, postextubation laryngospasm, bronchospasm, hypoxemia, nausea, vomiting, or any other complications were recorded (from the time of extubation till in PACU). Bucking was defined as a gag response with the ETT *in situ*. Coughing was defined as a gag response leading to forceful air expulsion with a sharp sound after the ETT was removed.

Sample size calculation: Due to the lack of similar studies conducted in the past for reference values of variance, this study was conducted as an exploratory pilot study with a total initial estimated sample size of 42 patients to be able to detect a difference of an empirical effect size of 0.8 for the time to achieve TOF ratio of 0.9 (one tailed), with 5% alfa error and 80% power. Post-hoc power analysis was performed for the final sample for noninferiority.

Statistical analysis: Data were recorded in MS Excel spreadsheet program. Graph pad Instat (Version 3.05) was used for data analysis. Descriptive statistics was expressed in the form of means/standard deviations or medians/ inter quartile range for numerical variables and frequencies and percentages for categorical variables. Data were presented graphically wherever appropriate for data visualization. Comparison for continuously distributed data was made using an independent sample *t*-test when comparing two groups. In nonnormally distributed data, appropriate nonparametric tests in the form of the Mann–Whitney U test were used for these comparisons. The Fisher's exact test was used for group comparisons of categorical data. $P < 0.05$ was considered statistically significant.

Results

A total of 50 patients were enrolled in the study and 42 patients, 21 in each group, were included in the final statistical analysis [Figure 2]. The demographic characteristics were similar in the two groups [Table 1]. Operative findings were also comparable in terms of duration of surgery, type of surgery, total atracurium, and fentanyl consumption during the surgery [Table 2]. The hemodynamic parameters, respiratory rate, and saturation were similar in both the groups at baseline, at the time of administering reversal, at extubation, and 5 min postextubation [Table 3].

In two patients in both groups, clinical conditions and awakening were achieved before reaching a TOF ratio of 0.9

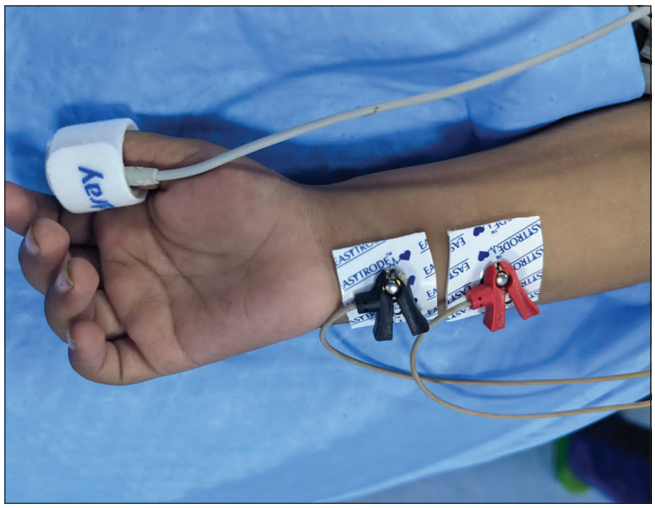

Figure 1: Attachment of probes for neuromuscular monitoring of ulnar nerve

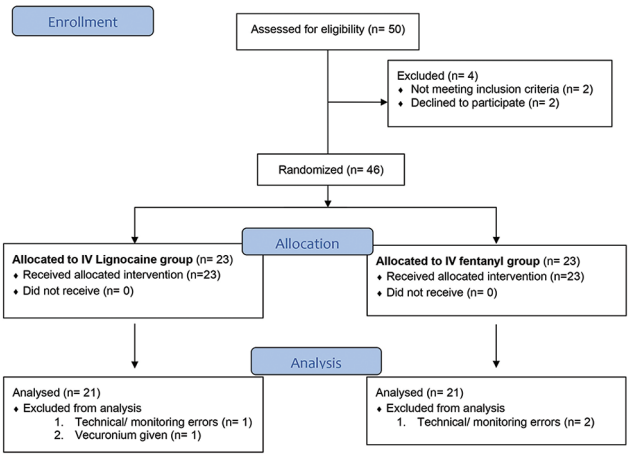

Figure 2: CONSORT flow chart

which warranted removing the tube at that point in time. These were included in the intention-to-treat analysis (ITT). The time to achieve a TOF ratio of 0.9 was similar in both groups analyzed by both ITT and per protocol ($n = 19$ in each group). Time to actual extubation was also similar (8.14 ± 3.31 min in LG vs 9.19 ± 2.89 min in FG [Table 2].

A higher proportion of patients experienced coughing at the time of extubation in the LG [5/21 (23.8%)], while the incidence of bucking was lower [2/21 (9.5%)] compared to FG [5/21 (23.8%)], $P = 0.41$. One patient in each group suffered laryngospasm and emergence delirium, which were successfully managed [Figure 3].

Post-hoc power analysis: in the control FG, the mean value of recovery times in terms of time to reach TOF of 0.9 was 6.65 ± 3.28 min. For a noninferiority limit of 3 min for LG compared to FG, with a 5% alpha error, a sample size of 21 in each group of the current study achieved a power of 90%.

Table 1: Comparison of demographic data

Characteristics	LG (n=21)	FG (n=21)	P
Age (Years)	4.64±2.28	5.24±2.14	0.389
Height (cm)	87.86±19.85	89.76±19.50	0.755
Weight (Kg)	16.85±6.08	17.79±7.05	0.649
Male	16/21 (76.2%)	16/21 (76.2%)	1.281
Female	5/21 (23.8%)	5/21 (23.8%)	

P<0.05 was considered significant, LG: Lignocaine group, and FG: Fentanyl group

Table 2: Comparison of intraoperative parameters and recovery characteristics

Characteristics	LG (n=21)	FG (n=21)	P
Time to 0.9 TOF (mins) (Intention to treat)	6.62±2.94	6.65±3.28	0.975
Time to 0.9 TOF (mins) (Per-protocol) (n=19 each)	6.79±3.03	6.79±3.31	0.999
Time to extubation (min)	8.14±3.31	9.19±2.89	0.281
Total Fentanyl (mcg)	39.19±21.44	42.14±24.42	0.668
Total atracurium (mg)	11.98±5.71	14.90±7.46	0.162
Duration of surgery (min)	106.67±58.83	107.09±45.67	0.979
Type of surgery			0.232
Abdominal surgery	7	9	
Orchidopexy	2	2	
Cystoscopy	7	1	
Ortho/soft tissue surgery	3	6	
Palate/lip	2	1	
Penile surgery	0	1	
Anal surgery	0	1	

P<0.05 was considered significant, TOF: Train of four, LG: Lignocaine group, and FG: Fentanyl group

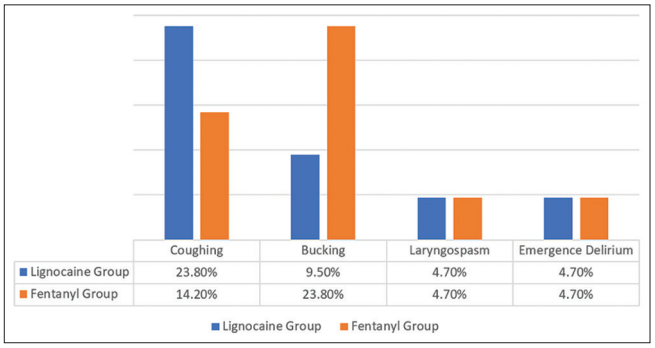

Figure 3: Comparison of incidence of respiratory and other adverse events

Table 3: Comparison of hemodynamics and respiratory parameters

Characteristics	Time Points	LG (n=21)	FG (n=21)	P
Heart rate	Baseline	106±21.02	102.05±19.41	0.530
	At reversal	108.85±20.54	117.28±20.48	0.191
	At extubation	119.57±20.73	126.71±28.49	0.359
	5 min post-extubation	108.80±23.03	119.33±26.17	0.174
Systolic blood pressure (mm Hg)	Baseline	94.52±12.84	98.81±15.56	0.338
	At reversal	99.85±10.05	105.71±14.06	0.129
	At extubation	107.24±10.52	112.71±13.72	0.155
	5 min post-extubation	101.43±14.72	104.76±12.79	0.438
Diastolic blood pressure (mm Hg)	Baseline	56.19±11.10	55.95±13.49	0.951
	At reversal	50.09±9.52	62.42±11.11	0.303
	At extubation	67.47±11.90	67.19±12.33	0.9395
	5 min post-extubation	60.76±12.39	63.05±10.45	0.522
Respiratory rate	Baseline	20.71±3.29	19.67±4.69	0.408
	At extubation	28.71±7.19	26.76±6.95	0.377
	5 min post-extubation	23.24±7.61	24±6.01	0.721
SPO_2 (%)	Baseline	99.28±0.46	99.52±0.51	0.183
	At reversal	99.23±0.62	99.23±0.62	0.989
	At extubation	99.52±0.51	99.47±0.60	0.908
	5 min post-extubation	99.42±0.51	99.57±0.59	0.364

P<0.05 was considered significant, LG: Lignocaine group, and FG: Fentanyl group

Discussion

PRAE are the leading cause of morbidity postoperatively. These include laryngospasm, bronchospasm, atelectasis, coughing, airway obstruction, hypoxia, stridor, and breath holding.[2] Among the drugs in the anesthesiologist's armamentarium, opioids, alpha agonists, and local anesthetic agents have been abundantly used as adjuvants to GA to reduce the incidence of coughing and bucking at the time of extubation.[15] Additionally, these drugs provide for better hemodynamics and smoother extubation conditions. Literature on adult patients has not come to a consensus on the effect of IV lignocaine on neuromuscular recovery.[6-9]

The present study was conducted to evaluate if lignocaine given prior to extubation prolongs the time taken to achieve a TOF ratio of 0.9 and time to extubation compared to giving fentanyl in children undergoing elective surgery. Both were found to be similar. Fentanyl was chosen as a comparator agent with the assumption that it does not directly affect neuromuscular recovery, although it may prolong the overall clinical recovery time. A review of the literature by Tung *et al*.[16] stated that intracuff instillation of lignocaine prolonged the extubation times when it was compared with placebo, dexmedetomidine, fentanyl, and remifentanil. In an animal model study by Braga *et al*., local anesthetics were found to show both pre- and postsynaptic effects and caused potentiation of the neuromuscular blockade caused by nondepolarizing neuromuscular blockers.[17] Lee *et al*.[9] investigated the interaction of cisatracurium and rocuronium with lignocaine on rat diaphragm and concluded that lignocaine increases the sensitivity as well as causes recurarization, which was clinically significant. In contrast to the above, Hans *et al*.[18] reported the time to spontaneous recovery of a TOF ratio ≥0.9 after a single intubating dose of cisatracurium when lignocaine infusion was administered as an adjuvant for surgery was 94 ± 15 min in the control group and 98 ± 16 min in the lignocaine group ($P = 0.27$), which was found to be insignificant. Most of the above-mentioned studies utilized lignocaine infusions, unlike the present study where a single shot dose was given before reversal.

A survey of the Society of Paediatric Anaesthesia on the use, monitoring, and antagonism of neuromuscular blockade found only 40% of practitioners assess blockade with neuromuscular monitoring in the pediatric population.[19] In the retrospective cohort trial, Klučka J *et al*.[20] studied 8046 pediatric patients who underwent surgery over one year and found a very low incidence of neuromuscular blockade monitoring (2.5%). The compatibility of existing monitoring devices with pediatric age groups seems to be the most probable reason for this underutilization. In another study, Klucka *et al*.[21] studied neuromuscular blockade in the pediatric population and found the incidence of the residual blockade to be 48.2% in the operation room and 26.9% in PACU, which is unacceptably high.

The meta-analysis published by Yang *et al*. states that the use of IV lignocaine perioperatively in adult patients decreased airway complications including coughing and sore throat without any increased risk of harm.[22] Furthermore, studies by Nishino *et al*. and Christensen *et al*. found lignocaine to be a safe cough suppressant.[23,24] Studies by Erb and Qi *et al*. present similar data in children.[4,5] In the present study, 5 out of 21 patients experienced coughing and only 2 patients experienced bucking in the lignocaine group. Similarly, opioids are routinely being used to prevent postoperative airway complications. Kireeti *et al*. also found low doses of fentanyl given prior to extubation in adults to be beneficial.[14] Three out of 21 patients experienced coughing at extubation and five patients suffered from bucking in the fentanyl group in the current study, which is in keeping with previous literature.

Limitations

This was a single-center pilot study. This result may be extrapolated to only healthy pediatric patients undergoing GA. Future trials may be planned with an appropriate sample size and in the subset of surgeries/children more prone to PRAE.

To conclude, the use of single-dose lignocaine before extubation of the trachea in pediatric patients is not associated with an increase in neuromuscular recovery time compared to fentanyl. Both fentanyl and lignocaine can be safely used in pediatric patients as modalities to prevent perioperative adverse respiratory events. Neuromuscular monitoring should be done in all pediatric patients undergoing surgery with neuromuscular blockade, if technically feasible.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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