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Research Article

COMPARATIVE EVALUATION OF FENTANYL AND LIGNOCAINE FOR REDUCTION OF INDUCTION DOSE OF PROPOFOL AND ATTENUATION OF HYPERTENSIVE RESPONSE TO LARYNGOSCOPY AND INTUBATION

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A B S T R A C T

Background: Propofol is a very popular and potent intravenous hypnotic agent. The major drawbacks of anaesthetic induction with propofol are a greater degree of hypotension and inadequate attenuation of the hypertensive response to intubation. In order to reduce these unwanted side effects, adjuvant agents like opioids or local anaesthetics may be used to decrease the propofol induction dose requirement.
Aims: Aims of our study were to compare the effects of fentanyl and lignocaine on Induction dose of propofol as well as on hypertensive response to laryngoscopy and intubation.
Study design: Randomized double-blind placebo-controlled study
Methods: We had randomized 90 adult patients of ASA grade I and II, aged 18 to 60 years, of either sex, weighing 40 to 80 kg, scheduled for elective surgery under general anaesthesia, into one of the three groups (n=30). Each patient received 2 ml of pretreatment solution over 5 seconds, followed one minute later by propofol injected @2.5 ml every 5 seconds and continued until loss of verbalization. **Group I:** 2 ml 2% lignocaine (40 mg); **Group II (fentanyl):** 2 ml fentanyl (100 µg); **Group III (placebo):** 2 ml normal saline. The total dose of propofol to achieve loss of response in each patient was recorded. HR and BP were monitored before laryngoscopy and 1, 2 and 5 minutes after laryngoscopy and every 15 minutes thereafter. All the data were recorded as frequencies and mean±SD. All the statistical operations were performed using Statistical Package for Social Sciences (SPSS) Version 13.0. Intergroup differences have been compared using chi-square test, ANOVA, student's "t" test and Mann-Whitney U test. The confidence level of the study has been kept at 95%, hence a "p" value <0.05 has been considered as statistically significant.
Results: The mean induction dose of propofol per unit body weight varied in the three groups significantly (p=0.033). In Group III, the quantity of propofol mixture given was 1.70±0.18 mg/kg followed by 1.67±0.26 mg/kg in Group I and 1.54±0.28 mg/kg in Group II. It was significantly higher in Group I as compared to Group II (p=0.031) and in Group III as comared to Group II(p=0.020) whereas no significant difference was seen between Groups I and III (p=0.938). There was no significant difference in mean HR among three groups at baseline as well as at different time intervals, the increase in HR being least significant in group II. A significant difference in MAP (p<0.05) was seen at 1 minute, 2 minutes, 5 minutes and 30 minutes after laryngoscopy, MAP being least in group II at all these points of time except at 5min.
Conclusions: Our study showed that fentanyl was much more effective in reducing the induction dose of propofol as compared to lignocaine when given 1 min before propofol. Also, fentanyl seemed to be effective in attenuating the HR response to laryngoscopy and intubation and was more effective than lignocaine in attenuating the hypertensive response to laryngoscopy.

INTRODUCTION

Propofol is a potent intravenous hypnotic agent which has become increasingly popular in the last two decades for the induction of anaesthesia. However, the major drawbacks of anaesthetic induction with propofol are a greater degree of hypotension as compared with other hypnotic agents and inadequate attenuation of the hypertensive response to intubation[1]. In order to reduce unwanted side effects of propofol, adjuvant agents may be used to decrease the propofol dose requirement during anaesthesia induction.

Studies have demonstrated that the propofol requirements for induction are reduced in the presence of an opioid [1]. Fentanyl has been studied extensively and is added during induction of anesthesia to provide analgesia during surgical procedures and to decrease the hypertensive response to intubation[2]. It is also known to potentiate the hypnotic effect of propofol [1]. Similarly, studies have also demonstrated that

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IV (or intra-muscular) administration of lignocaine significantly reduces the induction dose of propofol [3,4] and also reduces the hypertensive response to laryngoscopy and intubation. However, we didn't come across any research article comparing fentanyl and lignocaine for reduction of propofol dose required for induction. This study was planned to compare the effects of fentanyl and lignocaine on Induction Dose of propofol. Both fentanyl and lignocaine are integral components of balanced anaesthesia and have been shown to attenuate the response to laryngoscopy and intubation. Therefore, we used fentanyl and lignocaine doses consistent with those shown to reduce the cardiovascular stress of laryngoscopy and intubation and also studied their effects on hypertensive response to laryngoscopy and lntubation.

MATERIALS AND METHODS

After taking institutional ethical committee approval and obtaining written informed consent, 90 adult patients of ASA physical status I and II, aged 18 to 60years, of either sex, weighing 40 to 80kg, scheduled for elective surgery under general anaesthesia were enrolled for study which was conducted over a period of one year. Patients with deranged physiological parameters; history of cardiac, cerebrovascular, respiratory, hepatic or renal disease; history of adverse reaction to any of the study drugs; undergoing major vascular or cardiac surgery; patients with predicted difficult airway; pregnant and obese patients; hysterical patients or patients with difficulty in communication were excluded from the study.
After a thorough preanesthetic checkup and proper counselling, all patients were administered oral alprazolam 0.25 mg and oral ranitidine 150 mg on the night prior to surgery and were instructed to keep fasting for 8 hours pre-operatively.

On the day of surgery, patients' vitals were examined and investigation reports re-checked. In the operating room, routine monitors *i.e.* non-invasive blood pressure (NIBP), pulse oximeter (SpO_2), capnography (EtCO2) and electrocardiography (ECG) leads were connected and baseline readings were noted. Intravenous line was secured using a 20 gauge cannula in a vein on the dorsum of non-dominant hand. Each patient received 2 ml of pretreatment solution over a period of 5 seconds. One minute later, induction was done with propofol injected at a rate of 2.5 ml every 5 seconds and continued until loss of verbalization. Inability to respond to simple commands was used as the end-point of induction. The total dose of propofol to achieve loss of response in each patient was recorded. Patients were randomly allocated to one of the following three groups comprising of 30 patients each using a computer generated random number tables.

Group I (lignocaine): The pretreatment solution consisted of 2 ml of 2% lignocaine (40 mg)

Group II (fentanyl): The pretreatment solution consisted of 2 ml of fentanyl (100 μg)

Group III (placebo): The pretreatment solution consisted of 2 ml of normal saline

The pretreatment solution was prepared by an independent anesthesiologist and investigator was unaware of content of solutions. The data were collected by second, independent anesthesiologist who was unaware of group allocation.

After induction of anesthesia with propofol, tracheal intubation was facilitated with vecuronium bromide 0.1 mg/Kg. Heart rate (HR) and blood pressure (BP) were monitored before laryngoscopy and 1, 2 and 5 minutes after laryngoscopy and every 15 minutes thereafter. Anesthesia was maintained with inhaled technique supplemented with an opioid; and neuromuscular blockade was maintained with intermittent doses of vecuronium. At the end of surgery, decurarization was done by neostigmine 0.05 mg/Kg IV and glycopyrrolate 0.01 mg/Kg IV before extubating the trachea. Any adverse reactions during intra & postoperative period were also noted.

Statistical tools used

In the present study, the data has been represented as frequencies and mean values. For comparison of intragroup data, standard deviation has been used. Intergroup differences have been compared using chi-square test for proportions, analysis of variance (F-statistic) for comparing mean values of parametric data in more than two groups and student's "t" test for two groups. The mean values in a group at different time intervals have been compared using paired "t" test. For non-parametric data, such as pain score non-parametric equivalent of student's "t" test i.e. Mann-Whitney, U test has been used. The confidence level of the study has been kept at 95%, hence a "p" value <0.05 has been considered as statistically significant. All the statistical operations were performed using Statistical Package for Social Sciences (SPSS) Version 13.0.

Sample size calculation

Based on a previous study of comparison between midazolam and fentanyl for the reduction in propofol dose requirement by Delucia *et al*. [5], a sample size of 20 per group was calculated to detect a 25% reduction in dose, with 80% power and an alpha value of 0.05 for a three-level, one- way ANOVA. However, considering possible dropout, we included 30 patients in each group.

RESULTS

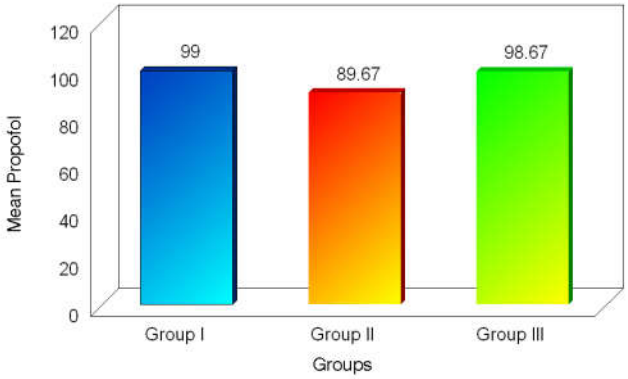
The groups were comparable with respect to age, weight, gender distribution and ASA grade of patients. [Table 1] A total of 14 patients (15.55%) belonged to ASA Grade II. Statistically there was no significant difference in ASA Grade wise distribution of patients in the three groups under study (p=0.553).

Table 1 Demographic profile of the patients

	Group I (n=30) (Lignocaine)	Group II (n=30) (Fentanyl)	Group III (n=30) (Placebo)	p-Value
Age (years)	38.77±13.13	42.70±12.36	36.03±12.23	0.125
Weight (kg)	60.13±10.90	59.15±9.42	58.37±9.65	0.791
Gender Male/Female	21/9	19/11	21/9	0.816
ASA Grade I/II	25/5	24/6	27/3	0.553

Table 2 Propofol induction dose

S.No.	Group	Propofol Induction Dose (mg) (Mean±SD)	F	"p"
1.	Group I (Lignocaine)	99.00±18.26		
2.	Group II (Fentanyl)	89.67±14.26	3.339	0.040
3.	Group III (Placebo)	98.67±14.79		

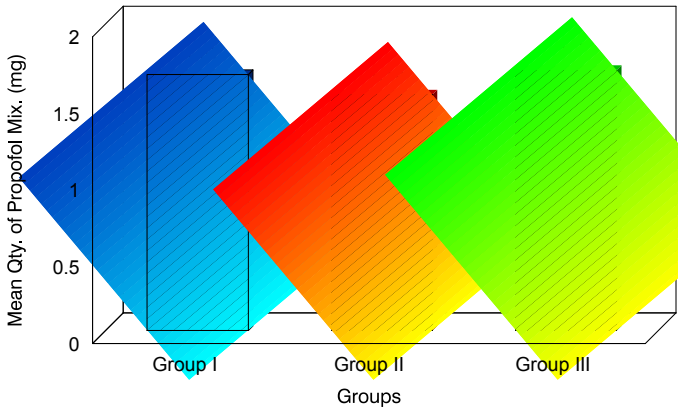


The mean propofol dose required for induction varied in the three groups significantly (p=0.040). In Group I, the mean induction dose of propofol was 99.00±18.26 mg followed by 98.67±14.79 mg in Group III and 89.67±14.26 mg in Group II. The mean induction dose of propofol per unit body weight also varied in the three groups significantly (p=0.033). In Group III, the quantity of propofol mixture given was 1.70±0.18 mg/kg followed by 1.67±0.26 mg/kg in Group I and 1.54±0.28 mg/kg in Group II. Intergroup comparison showed that in Group I, the quantity of propofol required for induction was significantly higher as compared to Group II (p=0.031) and it was higher in Group III as compared to Group II (p=0.020) whereas no statistically significant difference was seen between Group I and Group III (p=0.938).

There was no significant difference in mean heart rate among three groups at baseline as well as at different time intervals.[Table 5 &Fig 1] In placebo group, there was significant increase (p<0.05) in HR at 1min and 2min after laryngoscopy which settled there after. In lignocaine group, there was significant increase (p<0.05) in HR at 1min, 2min, 5min and 15min and a significant decrease (p<0.05) in HR much later. In fentanyl pretreatment group, there was no significant increase in HR except at 2min postlaryngoscopy.

Table 3 Propofol induction dose per kg body weight

S.No.	Group	Propofol Induction dose (mg/Kg) (Mean±SD)	F	"p"
1.	Group I(Lignocaine)	1.67±0.26		
2.	Group II (Fentanyl)	1.54±0.28	3.559	0.033
3.	Group III (Placebo)	1.70±0.18		



No significant difference in baseline MAP values was seen amongst the three groups. No significant difference in MAP values was seen amongst the three groups except at 1 minute, 2 minutes, 5 minutes and 30 minutes after laryngoscopy.[Table 6 &Fig 2] Thereafter there was no significant difference among the groups.

Table 4 Intergroup comparison of propofol induction dose

S.No.	Comparison	t	"p"
1.	Group I vs Group II (Lignoocaine vs Fentanyl)	2.206	0.031
2.	Group I vs Group III (Lignocaine vs Placebo)	0.078	0.938
3.	Group II vs Group III (Fentanyl vs Placebo)	2.399	0.020

Table 5 Comparison of heart rate in three groups at different time intervals

S.No.	Time Interval	Group I (Lignocaine)	Group II (Fentanyl)	Group III (Placebo)	F	p
1.	Baseline	89.87±12.09	90.40±13.05	86.80±14.32	0.652	0.524
2.	Pre Laryngoscopy	86.90±9.75	82.67±9.48*	84.33±11.04	1.335	0.269
3.	After 1 min	96.67±8.86*	93.37±10.29	94.60±8.84*	0.953	0.389
4.	After 2 min	96.63±8.54*	95.67±11.03*	95.53±9.18*	0.116	0.890
5.	After 5 min	93.97±9.14*	92.00±9.79	89.07±9.09	2.089	0.130
6.	After 15 min	93.67±13.69*	90.03±11.78	87.87±12.49	1.603	0.207
7.	After 30 min	90.00±11.88	89.83±12.28	87.33±14.71	0.395	0.675
8.	After 45 min	85.90±11.66	90.30±12.55	87.50±11.36	1.057	0.352
9.	After 60 min	85.52±13.01*	89.04±9.67	85.62±11.47	0.833	0.439
10.	After 75 min	77.93±11.63*	83.93±6.99	83.36±11.78	1.481	0.240
11.	After 90 min	78.10±12.12*	86.20±5.40	83.86±11.70	1.107	0.351

Difference from baseline *p<0.05

Table 6 Comparison of MAP in three groups at different time intervals

S.No.	Time Interval	Group I (Lignocaine)	Group II (Fentanyl)	Group III (Placebo)	F	p
1.	Baseline	100.47±11.89	97.39±8.63	98.02±12.68	0.631	0.534
2.	Pre laryngoscopy	84.70±11.09*	79.68±7.76*	85.04±9.46*	2.977	0.056
3.	After 1 min	102.20±12.59	95.58±11.11	104.36±13.81*	3.983	0.022
4.	After 2 min	94.24±11.45*	92.28±10.94*	99.91±12.67	3.437	0.037
5.	After 5 min	85.97±10.62*	86.42±9.20*	92.97±12.23*	3.976	0.022
6.	After 15 min	96.70±12.85*	91.59±8.32*	94.48±11.74	1.589	0.210
7.	After 30 min	103.51±13.73	95.76±8.87	99.16±12.93	3.132	0.049
8.	After 45 min	101.41±15.50	97.64±9.99	103.73±9.69*	1.957	0.147
9.	After 60 min	100.54±11.51	95.32±7.00	101.05±10.38	2.852	0.064
10.	After 75 min	95.38±12.29	97.05±6.98	103.08±8.52*	2.407	0.103
11.	After 90 min	100.83±11.18	95.20±6.89	101.10±9.04*	0.672	0.523

Difference from baseline *p<0.05

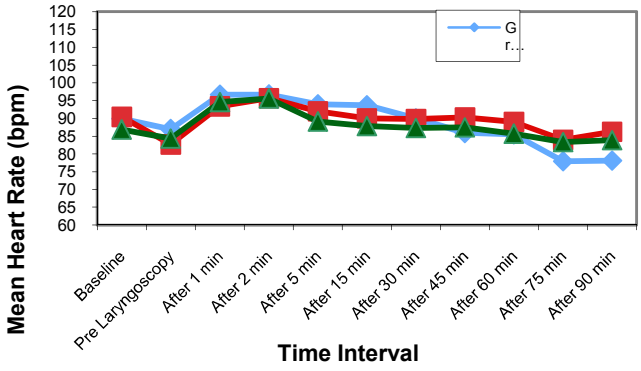


Fig 1 Mean heart rate in three groups at different time intervals

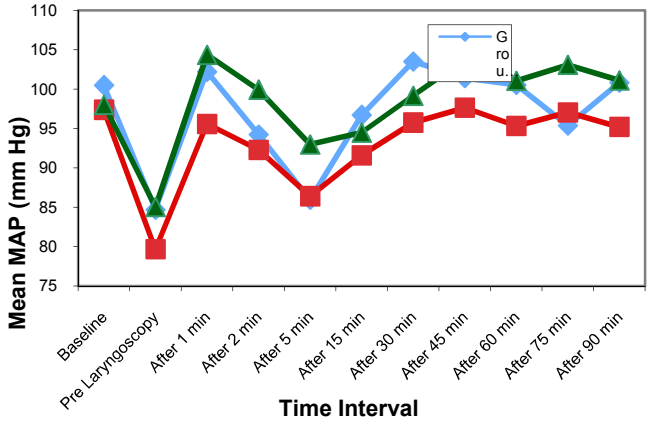


Fig 2 Mean arterial pressure in three groups at different time intervals

DISCUSSION

Many investigators have extensively studied the hypnotic dose of propofol during the induction of anaesthesia, and have found a variety of factors that affect the dose required to achieve hypnosis [6]. These include patient's age [7], sex [8], body weight [9], the rate of infusion [10,11], coadministered drugs [6,12] and anxiety [13]. These phenomena can be partly explained by their effects on pharmacokinetics, which modulate the concentration of propofol. Various synergistic drugs that are coadministered for this purpose are methylene blue,β-adrenergic blockers (esmolol),α_2-adrenergic agonists (dexmedetomidine, clonidine), magnesium, opioids (fentanyl, alfentanyl),barbiturates, local anaesthetics (lignocaine, bupivacaine) and benzodiazepines such as midazolam and ketamine [6].

Similarly, coadministration of many drugs with induction agent aims to reduce the haemodynamic response due to intubation and laryngoscopy which include local anesthetics (lignocaine), opioids (fentanyl), β-adrenergic blockers, vasodilators (nitroglycerin, sodium nitroprusside), calcium channel antagonist (diltiazem), α_2-adrenergic agonists (dexmedetomidine) and combinations of these drugs [14]. Fentanyl and lignocaine are two such drugs which are co-administered with propofol for both the purposes i.e., reduction of induction dose requirement of propofol as well as attenuation of the hemodynamic response to laryngoscopy and intubation. In our study, we have compared these two drugs for both these effects.

The results of our study show that Fentanyl was much more effective in reducing the induction dose of propofol as compared to lignocaine when given 1 min before propofol and this difference was statistically significant (t=2.206; p=0.031). Fentanyl 2 µg/kg given 1 min before propofol significantly reduced the induction dose of propofol from 1.70±0.18 mg/Kg to 1.54±0.28 mg/Kg (t=2.399; p=0.020). The results of the present study are consistent with the results of previous studies by Lysakowski *et al* [1] and Mi *et al* [15].

Lysakowski *et al*. [1] had showed that analgesic concentrations of fentanyl facilitate loss of consciousness at lower plasma effect-site concentrations of propofol. Their finding supports the results of our study even though we didn't measure the plasma effect-site concentrations of propofol. Mi *et al*. [15] also found lower propofol concentrations in the propofol + fentanyl group compared with the propofol group at loss of responsiveness to verbal commands and loss of eyelash reflex. They had concluded that fentanyl pre-treatment potentiated the effect of propofol for achieving the hypnotic end-point. In their study, pre-treatment with fentanyl 2 µg/kg reduced the induction dose of propofol to 1.1±0.50 mg/kg which is even lower than that in our study (1.54±0.28 mg/Kg). The difference in mean propofol doses may be the result of different methods which were used for obtaining the hypnotic dose of propofol. The decrease in the propofol induction dose associated with fentanyl administration is consistent with published data on the effect of fentanyl in animal studies as well [16,17].

Pretreatment with lignocaine also reduced the induction dose of propofol in our study which is in agreement with many other studies done previously. Kelsaka E *et al*. [3] had done a study to compare the effects of intramuscular and intravenous Lignocaine on propofol induction dose in which they had found that IV lignocaine 1.5 mg/kg given 2 min before anaesthesia induction significantly reduced the induction dose of Propofol from 2.1±0.2 mg/kg to 1.58±0.3 mg/kg ($p<0.001$) without any clinically important side effects. In our study, pretreatment with lignocaine 40mg 1 min before induction could only mildly reduce the induction dose requirement of propofol from 1.70±0.18 mg/kg to 1.67±0.26 mg/kg which was not statistically significant (t=0.078; p=0.938). This difference might be because of a much higher dose of lignocaine used by them (1.5 mg/Kg) and a longer duration to induction in their study as compared to ours (2min vs. 1min).

In our study, fentanyl seemed to be effective in attenuating the HR response to laryngoscopy and intubation [Table 5]. This is in agreement with many other studies done earlier. Though there was a significant decrease in HR immediately after induction with propofol (before laryngoscopy) but this didn't warrant any corrective action and settled within a minute. Also, fentanyl was more effective than lignocaine in attenuating the hypertensive response to laryngoscopy [Table 6]. No significant difference in baseline MAP values was seen amongst the three groups. A significant difference ($p<0.05$) was seen at 1 minute, 2 minutes, 5 minutes and 30 minutes after laryngoscopy, MAP being least in the fentanyl group at all these points of time except at 5min.

The effects of propofol on the central nervous system involve pre- and postsynaptic effects, resulting from actions at multiple cellular and molecular sites [18]. The major action of propofol appears to be mediated by facilitation of inhibitory transmission by activating the postsynaptic $GABA_A$ receptor-chloride ionophore complex [18,19,20]. Calcium influx is also modulated through slow calcium channels and inhibits voltage-gated sodium currents [18,21,22]. Lignocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby affecting local anaesthetic action. Local anaesthetics also potentiate GABA-mediated Cl^-currents by inhibiting GABA uptake [23]. Similar mechanisms of action of both propofol and lidocaine may explain the additive effect of these agents in reducing the hypnotic dose. Sentruk *et al*. [4] had concluded that systemic general anaesthetic effects of absorbed local anaesthetics play an important role in the reduction of the dose of the general anaesthetic.

Fentanyl acts as agonist at opioid receptors present at presynaptic and postsynaptic sites in the central nervous system (CNS) and outside the CNS in peripheral tissues [24]. Out of the various types of opioid receptors (*i.e.*μ, δ and κ), fentanyl predominantly acts on μ-receptors. The action is mediated by C protein coupled adenylate cyclase system. There is inactivation of voltage dependent calcium channels and increase in conductance of potassium channels. Opioid receptors are distributed in pre and postsynaptic sites in the central nervous system and in the peripheral afferent neurons. Fentanyl mimics the actions of endogenous opioids resulting in pain modulation. The primary effect is reduction in neurotransmission [25]. At high doses, it inhibits the uptake of nor-adrenaline by neurons. These effects somewhat explains the reduction in induction dose of propofol caused by fentanyl. Differences among studies may be attributed to dissimilarities in experimental design including the speed of propofol administration and intubation criteria.

A major limitation of our study is that the plasma concentration of propofol were not measured directly. A real-time analysis of plasma propofol concentrations would have been helpful to assure a steady state [26]. Another potential limitation is that we did not measure Bispectral (BIS) or Entropy (SE/RE) indices which are widely used to estimate the depth of anesthesia and sedation. The reason behind it is that administration of opioids together with anaesthetics may substantially change the predictive value of these EEG monitors. Sebel *et al*. [27] had reported that the use of an opioid analgesic as adjunct confounds the results of BIS as a measure of anaesthetic adequacy when using movement response to skin incision as the primary endpoint. Mi *et al*. [15] found higher BIS in the propofol + fentanyl group compared with the propofol group at unresponsiveness to verbal commands, loss of eyelash reflex and response to mechanical nasal membrane stimulation.

CONCLUSIONS

In conclusion, pre-treatment with fentanyl 2 μg/kg was associated with a clinically important decrease in the induction dose of propofol as well as attenuation of responses to laryngoscopy and intubation without producing haemodynamic instability. Further studies are warranted to determine if there is a ceiling to the effect of fentanyl on the induction dose of propofol and on attenuation of responses to laryngoscopy.

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