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Atracurium for Rapid Sequence Induction; A Dose Determining Randomized Control Trial at a Tertiary Care Hospital

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Author`s Contribution

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ABSTRACT

Objective: To find out the efficacy of 3-4 ED95 dose of Atracurium in providing optimal intubating conditions for Rapid Sequence Induction.

Methodology: Single-blind randomized control trial was carried out Department of Anesthesia and Critical Care Medicine, Pakistan Institute of Medical Sciences (PIMS), Islamabad. 118 patients were included and divided into two groups by help of computer-generated random numbers. All the patients were pre-medicated with 8 mg of IV Dexamethasone. Group A patients received 1 mg/kg while group B patients received 0.75 mg/kg of Atracurium. Intubating conditions were assessed on the basis of number of coughing episodes along with degree of vocal cord movement or paralysis.

Results: Patients who received 0.75 mg/kg of Atracurium had statistically significant better intubating conditions as compared to those receiving 1 mg/kg of Atracurium (p value < 0.05). Coughing episodes were more common among patients receiving higher dose of Atracurium while degree of vocal cord paralysis was similar in both groups. Furthermore 75% of histamine related adverse effects such as erythema and bronchospasm were observed in higher dose group. The difference was statistically significant with a p value of <0.05.

Conclusion: Atracurium at a dose of 0.75 mg/kg along with pre-medication with 8 mg of IV Dexamethasone provided better and safer intubating conditions for rapid sequence induction.

Keywords: Atracurium, Rapid Sequence Induction, Aspiration, Airway Management, Anesthesia

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Introduction

Expert airway management is one of the essential skills required by the anesthetist. It ensures effective ventilation and oxygenation of the patient. It can be provided via non-invasive devices such as nasal cannula, face mask or venturi mask. In an anesthetized patient, airway management is done by the help of invasive devices such as endotracheal tube (ETT) or laryngeal mask airway (LMA). In individuals with risk of aspiration; securing the airway by the help of endotracheal tube is required.[1,2] ETT placement results in manipulation of the vocal cords thereby requiring muscle relaxation.[1] Aspiration is one of the lethal peri-operative complications related to anesthesia having wide range of effects. It can cause obstruction of major airways resulting in atelectasis, aspiration pneumonitis i.e. chemical burning of tracheobronchial tree and lung parenchyma or it can be severe enough to cause acute respiratory distress syndrome (ARDS).[3] All of this results in increased peri-operative morbidity and mortality. Furthermore, aspiration can still occur in apparently fasted individuals. However the sequalae may not be as severe as those without fasting.[4] In a review of 4000 incidents of aspiration, 67% of the patients were adequately fasted but still suffered from this catastrophic event in the peri-operative period. Aspiration resulted in significant harm in more than 50% of the cases and caused death in 6.6% of the cases[5] Similarly in closed

claim project of American Society of Anesthesiologist (ASA) death and permanent severe injury were common outcomes of peri-operative aspiration. ASA closed claim project revealed that death occurred in 57% of the cases while anesthesia care was substandard in 59% of the cases of aspiration.[6] Apart from short term effects on peri-operative morbidity and mortality; the long-term prognosis of aspiration pneumonia was also found to be poor. 80.2% of the patients who had suffered from aspiration died during follow up at 50.7 weeks while 1 year mortality was also significantly high at 49%.[7] Similarly it was found that diagnosis and successful management of Aspiration Pneumonia can be difficult due to overlapping features with hospital acquired pneumonia and there is significant presence of anti-microbial resistance.[8]

Therefore, from above mentioned facts it is clear that prevention of aspiration is the key to better outcome. One way to prevent aspiration is to rapidly secure the airway with the help of ETT. This technique of rapidly securing the airway in individuals at risk of aspiration is known as rapid sequence induction and intubation (RSII). RSII usually provides optimal intubating conditions within 1 minute after induction of anesthesia.

IV hypnotic drug such as Propofol along with a rapid acting muscle relaxant is used for RSII. Of the commonly used muscle relaxants Succinylcholine and Rocuronium are used for RSII. Succinylcholine a depolarizing neuromuscular blocker, when given at a dose of 1.5 mg/kg causes profound neuromuscular paralysis within 1 minute with paralysis lasting for 5-15 minutes. However it can cause hyperkalemic cardiac arrest among burn patients and those with neurological deficits.[9,10] Therefore, alternative neuromuscular blockers are required to secure airway in such patients. Rocuronium when given at a dose of 1.2 mg/kg provides optimal intubating conditions within 60seconds and can be used for RSII. Its effects can be rapidly reversed with sugammadex and hence lethal scenario of cannot intubate and cannot ventilate can be avoided.[11,12] Sugammadex forms complex with Rocuronium which is eliminated by the kidneys. Prolong neuromuscular blockade following Rocuronium administration is possible among patients suffering from renal impairment.[13,14] Furthermore, Rocuronium-Sugammadex complex causes anaphylactic reaction in about 1 in 2500 cases.[15] Similarly, when Rocuronium was used for RSII among patients suffering from myocardial infarction it resulted in higher mortality. [16] Furthermore, Sugammadex i.e. reversal for Rocuronium is not widely available because of its high manufacturing costs. Therefore, one can clearly see that Rocuronium and Succinylcholine are not ideal agents for RSII. An ideal or near ideal agent will be the one that is widely available along with its reversing agent, having organ independent elimination and is relatively cardiovascular stable. One of the drugs having some of the above-mentioned properties is Atracurium; a non-depolarizing neuromuscular blocker. It has been used widely in anesthesia practice because of its organ independent Hoffman elimination and relatively lower incidence of cardiovascular side effects.[17] Atracurium has an intubating dose of 0.5 mg/kg which provides optimal intubating conditions within 3 minutes.[17] However, if given at a dose 3-4 times of ED 95 i.e., the dose requires to dimmish muscle twitch response height by 95%, it may aid fast tracheal intubation. ED 95 of Atracurium in adult patients is 0.23 mg/kg.[18] Therefore, a dose of 0.75 mg/kg or 1 mg/kg can be utilized for RSII. Till date very limited literature is available regarding the use of Atracurium for this purpose. One of the study conducted recently has shown that when Atracurium is given at a dose of 1 m/kg or 0.75 mg/kg it can be provide fast and satisfactory intubating conditions within 1 minute.[19] Therefore, it can be used as an alternative neuromuscular blocker for rapid sequence induction.

Our single-blind randomized control trial investigated the dosage, efficacy and side effects of the two relatively high doses atracurium (1m/kg vs 0.75 mg/kg) in conjunction with Dexamethasone, Propofol and Fentanyl for rapid sequence anaesthetic induction.

Methodology

After approval from Ethical Review Board, this single-blind randomized control trial based was carried out department of Anesthesia and Critical Care Medicine, Pakistan Institute of Medical Sciences (PIMS), Islamabad from 7th April, 2023 to 7th October, 2023. The total sample size was 118 which was calculated according to formula ($n= \{Z_{1-a/2} \sqrt{2P}(1-P) Z_{1-\beta} \sqrt{P_1(1-P_1) + P_2(1-P_2)}\}^2 / (P_1+P_2)^2$) by taking level of significance 5%, power of test to be 80% and P1= 0.514 and P2= 0.263(19). Patients fulfilling the inclusion criteria i.e., Age: 18 years and above, American Society of Anesthesiologists (ASA) class: 1 & 2, elective surgery under general anesthesia and surgery duration greater than 1h were enrolled in the study. The patients having unstable hemodynamic status, neuromuscular disease, Ischemic Heart disease, Asthma and COPD, potentially difficult airway, BMI ≥25.0 kg/m^{2,} Head and Neck surgeries were excluded from the study. The enrolled patients were divided into two groups using

computer generated random numbers. Group A patients received 1 mg/kg of Atracurium while group B patients received 0.75 mg/kg of Atracurium. After arriving in the Operating Room (OR) standard ASA monitoring was attached and patients were pre-oxygenated using a tightly fitted face mask with 5L of Oxygen for 3 minutes. Afterwards patients were given 1 Mcg/kg of Fentanyl and 8mg of IV Dexamethasone. Patients were then immediately knocked out by 2 mg/kg IV bolus dose of Propofol. This was immediately followed by the intravenous administration of different doses of Atracurium over 30 seconds guided by the intervention group. The doses of Atracurium were prepared by different anesthetist in 20 ml syringe. Intubation was performed after 1 minute by a well-trained anesthetist; having an experience of at least 3 years. The intubating anesthetist was blinded to dose of Atracurium. The anesthetist intubating the patient graded the intubating conditions as follows:

Degree of coughing or bucking:

1. Excellent: No coughing or bucking and easy passage of endotracheal tube (ETT).
2. Good: Slight coughing (1-3 episodes) or bucking during passage of ETT.
3. Fair: Moderate coughing (4-5 episodes) or bucking during passage of ETT.
4. Poor: Vigorous coughing (≥6 episodes) or bucking and unable to pass ETT.

Degree of vocal cord paralysis:

5. Excellent: No movement of vocal cords
6. Good: Slight movement of vocal cords
7. Fair: Moderate movement of vocal cords
8. Poor: Vigorous movements of vocal cords and not being able to pass ETT.

After induction of anesthesia and securing of airway by endotracheal tube, depth of neuromuscular blockade was assessed by acceleromyography using Train of Four (TOF) count. Time of recovery of neuromuscular blockade was noted for both groups.

General Anesthesia was maintained with 40% Oxygen, 60% Nitrous Oxide and with volatile anesthetics (Isoflurane/Sevoflurane). Patients were be mechanically ventilated using lung protective volume control ventilation. End-tidal Carbon dioxide ($EtCO_2$) was kept between 35-45 mm of Hg. Blood pressure, heart rate, and pulse oximeter readings were noted at 1-minute intervals during peri-induction period and then every 3 minutes till the end of surgery.

Any hemodynamic instability i.e., greater than 20% deviation from baseline blood pressure or heart rate and rise in peak airway pressures or side effects resulting from high dose of atracurium such as cutaneous flushing, rash, bronchospasm, were noted and managed accordingly.

Results

Out of 118 patients; 72(61%) were male while rest were female. 56.8% of the patients labelled as ASA I while rest were labelled as ASA II. Minimum age of presentation was 18 years while maximum was 70 years. Mean age of presentation was comparable in both groups. Mean age in group A was 31.10 ± 11.94 years while in group B it was 30.05 ± 13.16 years. Details of Intubating conditions encountered in both groups are shown in table I.

Furthermore, in patients suffering from cough only 7.1% had more than 20% variation in hemodynamics from baseline indicating that adequate depth of anesthesia was achieved before laryngoscopy and intubation. It means that coughing was not due to light plane of anesthesia. Regarding adverse events particularly histamine related; 75% of these events occurred in Group A. The difference was statistically significant with a p value of 0.014. Among patients receiving 1mg/kg of Atracurium; 15.3% suffered from erythema while in Group B the incidence was noted to be 8.5%. Furthermore, all of the patients who had erythema showed a drop in blood pressure by more than 20% from baseline along with a significant tachycardia. This was successfully managed with 50-100 Mcg IV bolus dose of Phenylephrine. Bronchospasm only occurred in Group A with incidence being 10.2%.

Table I: Intubating Conditions among patients receiving two different doses of Atracurium

Intubating conditions			Group A 1 mg/kg	Group B 0.75 mg/kg	P-value (Chi Square Test)
Coughing	No Cough	Excellent	54.2%	74.6%	P= 0.021
	Cough Positive	Good	23.7%	13.6%	
		Fair	11.9%	0.0%	
		Poor	10.2%	11.9%	
Vocal cord movements		No Movement	93.2%	89.8%	P= 0.563
		Slight	0%	1.7%	
		Vigorous	6.8%	8.5%	

Bronchospasm was successfully managed by 30-50 mg IV bolus dose of Propofol.

Furthermore, degree of Hemodynamic stability among two groups is shown in table II.

Hemodynamics were comparable among two groups. All of the patients who had hemodynamic instability showed a more than 20% fall in blood pressure and a rise in heart rate from pre induction values. This hemodynamic instability was seen on induction with IV agents. Furthermore, 65% of the patients who had clinically significant hypotension and tachycardia had concomitant erythema. All of the hemodynamically unstable episodes responded successfully to phenylephrine IV bolus dose of 50-100 Mcg.

Mean duration of neuromuscular blockade as assed by acceleromyography train of four (TOF) count following induction dose was 78.12±20.53 minutes in group A while it was 48.9±8.90 minutes among group B members.

Table II: Hemodynamic profile or stability among two groups.

Hemodynamic Profile	Group A	Group B	P value (Chi Square Test)
Hemodynamic variables ≤ 20% variation from baseline	76.3%	86.4%	P= 0.156
Hemodynamic variables ≥ 20% variation from baseline	23.7%	13.6%	

Discussion

This single blind randomized control trial provides an insight regarding RSII. Over the years Atracurium has been used in anesthesia practice but only a limited data is available for its use in RSII. Our study shows that vocal cords were completely paralyzed in 94.9% of the patients receiving 1mg/kg dose of Atracurium as compared to 89.8% patients who received 0.75 mg/kg of Atracurium (p value >0.05). Our results are comparable with the available literature which reveals a vocal cord paralysis rate of 94.9% among 1 mg/kg atracurium group and 94.6% among 0.75 mg/kg group.[19] Both 1 mg/kg and 0.75 mg/kg of Atracurium doses provided excellent to good intubating conditions with respect to cough in 77.9% and 88.2% of patients respectively. In the previous study the intubating conditions were good to excellent in 86.5% of the 1 mg/kg atracurium group patients and in 84.6% of the 0.75 mg/kg group patients.[19] The incidence of cough in available literature was comparable in both groups.

However, in our study the incidence of cough was significantly higher among patients receiving 1mg/kg of Atracurium. The p value is 0.023 that is statistically significant. This could be due to ceiling effect of Atracurium dose or it can be due to successful blunting of histamine effects as the patients in our study were premedicated with 8 mg of IV Dexamethasone. It has been shown that time of onset of action of IV Dexamethasone is rapid and instantaneous.[20] Furthermore at a dose of 8mg/kg; Dexamethasone has been shown to provide potent anti-inflammatory effects along with analgesia and prophylaxis against post operative nausea and vomiting.[21,22] The anti-inflammatory effects of Dexamethasone may have decreased the incidence of cough in patients receiving 0.75 mg/kg of Atracurium.

While such dose of Dexamethasone may have fallen short to prevent this potential side effect among patients receiving higher dose of Atracurium. This is further supported by the fact that patients receiving 1mg/kg Atracurium intravenously had higher incidence of other potential histamine related adverse effects such as erythema and bronchospasm. 75% these events occurred in patients receiving 1mg/kg of Atracurium. The difference was statistically significant with p value of 0.014. Incidence of erythema was 15.3% among patients of group A members as compared to 8.5% among group B members. In the previous study erythema occurred 21.6% in 1mg/kg group while it was 17.9% in 0.75 mg/kg group.[19] The decreased incidence of erythema observed in our study can be due to pre-medication with 8mg IV Dexamethasone. In our study incidence of bronchospasm was 10.2% among group A members while none of the patients in group B developed bronchospasm. This further reinforces the concept of Atracurium dose dependent histamine release and its adverse effects. However in the already available literature none of the patients developed bronchospasm in the peri-induction period.[19] The difference seen can be due to difference in genetic susceptibility of geographically different population to develop bronchospasm upon exposure to Atracurium.

Furthermore, in our study during the peri-induction period; clinically significant hypotension and tachycardia occurred in 25.4% of the patients who received 1mg/kg of Atracurium while the incidence was 13.6% among the patients receiving 0.75 mg/kg of Atracurium (p value >0.05). 65% of the patients who had clinically significant hypotension and tachycardia had concomitant erythema. This means that hemodynamic instability might have been caused by histamine release. This is again supported by the

already available literature which reveals greater degree of hemodynamic instability among patients receiving 1mg/kg dose of Atracurium with difference being statistically significant (p value < 0.05).[19] There was some degree of difference in duration of neuromuscular blockade following induction dose of Atracurium observed in our study from the observations made by Chalermkitpanit P et al.[19] Mean duration of neuromuscular blockade as assessed by TOF count following induction dose was 78.12±20.53 minutes among patients receiving 1 mg/kg of Atracurium while it was 48.9±8.90 minutes among those receiving 075 mg/kg of Atracurium. In the previous study it was found to be 80.9±14.3 minutes among patients receiving 1 mg/kg of Atracurium while it was 70.7 ± 13.9 in case of 0.75 mg/kg of Atracurium.[19] The difference can be due to the difference in drug quality as well as variation in drug metabolism in geographically different population.

Conclusion

Atracurium at a dose 3-4 times ED95 can provide rapid and effective neuromuscular blockade for rapid sequence induction. A dose of 0.75 mg/kg of Atracurium was found to be safer when compared to a dose of 1mg/kg of Atracurium. Furthermore, premedication with 8 mg of IV Dexamethasone immediately before induction of Anesthesia can reduce the incidence of potential histamine related adverse effects.

Limitation of study: This study did not involve pediatric population, pregnant females as well as those patients who were overweight or obese. Further studies are required to study the effect of Atracurium in rapid sequence induction in above mentioned population.

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