

RANDOMIZED CLINICAL TRIAL TO COMPARE THE INCIDENCE OF RESIDUAL NEUROMUSCULAR BLOCK FOLLOWING PANCURONIUM AND ATRACURIUM USING TRAIN OF FOUR RATIOK. A. Nagesha¹, A. S. Nagaraja²**HOW TO CITE THIS ARTICLE:**

K. A. Nagesha, A. S. Nagaraja. "Randomized Clinical Trial to compare the Incidence of Residual Neuromuscular Block following Pancuronium and Atracurium using Train of Four Ratio". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 17, April 28; Page: 4676-4682, DOI: 10.14260/jemds/2014/2495

ABSTRACT: BACKGROUND: Several clinical studies have reported that significant number of patients receiving non depolarizing muscle relaxants during general anesthesia show postoperative residual neuromuscular block when assessed by neuromuscular monitor in the recovery room. The degree of residual neuromuscular block produced by non-depolarizing muscle relaxants can be evaluated by clinical tests as well as by neuromuscular monitoring y neuromuscular monitor in the recovery room. A randomized double blind clinical trial to determine and compare the incidence of postoperative residual neuromuscular block in patients receiving pancuronium and atracurium applying Train of Four ratio using Train of Four- Guard neuromuscular monitor. **AIMS AND OBJECTIVES:** To compare the incidence of postoperative residual neuromuscular block following pancuronium and atracurium using Train of Four Ratio in the recovery room. **MATERIALS AND METHODS:** Comparative randomized study done using 100 patients of age between 15-60 years belonging to either sex, ASA grade 1 and 2 with GROUP 'P' – Pancuronium was employed as the muscle relaxant, GROUP 'A' – Atracurium was employed as the muscle relaxant. Statistical analysis done using student "t" test. **RESULTS:** The mean duration required to attain Train of Four Ratio of 0.80 in patients with initial Train of four ratio <0.80 in group 'P' was 9.65±5.4413 min and in group 'A' was 2.8± 1.4832 min. **CONCLUSION:** 1. Our study concludes that the incidence of residual neuromuscular block in patients receiving pancuronium and atracurium were 40% and 10% respectively. Thus residual neuromuscular block can be a significant problem in recovery room, during the postoperative period. 2. The use of intermediate acting non depolarizing muscle relaxant like atracurium lowers the incidence of residual neuromuscular block but does not eliminate it.

KEYWORDS: Residual Neuromuscular Block, Train of Four, Pancuronium, Atracurium.

INTRODUCTION: Several clinical studies have reported that significant number of patients receiving non depolarizing muscle relaxants during general anesthesia show postoperative residual neuromuscular block when assessed by neuromuscular monitor in the recovery room.^{1, 2} Postoperative residual neuromuscular block has been one of the important causes of mortality and morbidity related to anaesthesia.³

It was postulated that the use of the intermediate acting neuromuscular blocking agent would be associated with a lower incidence of residual neuromuscular block.⁴

Among these, atracurium due to its spontaneous degradation in the plasma was expected to ensure a more complete state of recovery.⁵

The degree of residual neuromuscular block produced by non-depolarizing muscle relaxants can be evaluated by clinical tests as well as by neuromuscular monitoring.^{6, 7}

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Neuromuscular monitoring using train of four stimulation correlated well with clinical signs of recovery in healthy patients undergoing elective surgeries.⁸

It has been suggested that a train of four ratio >0.80 is necessary to ensure safety in the postoperative period.^{9,10}

We therefore conducted a randomized double blind clinical trial to determine and compare the incidence of postoperative residual neuromuscular block in patients receiving pancuronium and atracurium applying Train of Four Ratio, using Train of Four - Guard neuromuscular monitor.

AIMS AND OBJECTIVES: To compare the incidence of postoperative residual neuromuscular block following pancuronium and atracurium using train of four ratio in the recovery room.

MATERIALS AND METHODS:

STUDY DESIGN: Comparative randomized study was conducted after obtaining approval of institutional ethical committee and informed written consent from all the patients.

SAMPLE SIZE: 100 Patients of age between 15-60 years belonging to either sex, ASA grade 1 and 2.

SAMPLING METHOD: Prospective randomized study

STATISTICAL ANALYSIS: Student "t" test

INCLUSION CRITERIA:

- 1) Patients of either sex of ASA grade 1 and 2
- 2) Age 15-60 years
- 3) General anaesthesia for elective surgery with tracheal intubation and mechanical ventilation
- 4) Surgery of duration 60- 180 minutes

EXCLUSION CRITERIA:

- 1) Hypothermic < 36° c
- 2) Patients whose trachea were to remain intubated after surgery
- 3) Patients in whom neuromuscular block not reversed with neostigmine
- 4) Disorders of liver, kidney, endocrines and neuromuscular junctions.

STUDY GROUPS:

GROUP 'P' – Pancuronium was employed as the muscle relaxant

GROUP 'A' – Atracurium was employed as the muscle relaxant

The patients were investigated preoperatively and following investigations were done if found necessary.

- 1) Hemoglobin estimation
- 2) urine routine
- 3) RBS
- 4) Blood urea, serum creatinine
- 5) Serum albumin, bilirubin
- 6) Chest x-ray, ECG.

All the patients were premedicated with atropine 0.01mg/kg, midazolam 0.05 mg/kg and fentanyl 1-2 micrograms/kg intravenously.

Before inducing the patient oxygenation was done for three minutes with 100% oxygen.

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Induced with injection thiopentone sodium 5mg/kg. The tracheal intubation was done under muscle relaxation by suxamethonium 1.5mg/kg IV. Anesthesia was maintained with the muscle relaxant, oxygen, nitrous oxide and halothane [0.5% - 1%], the neuromuscular monitoring was not used intraoperatively. The name of the non-depolarizing muscle relaxant used, the total dose of it used and the total time elapsed from the last dose of non-depolarizing muscle relaxant till the reversal were not recorded on the anesthesia chart, but were recorded separately, This was done to ensure that the anesthesiologist in charge of the recovery room remains blinded as to these details.

After the surgery, neuromuscular block was reversed with atropine 0.02 mg / kg and neostigmine 0.05 mg /kg and the patient was extubated and then shifted to the recovery.

In the recovery room as soon as the patient was received, TOF Guard neuromuscular monitor was attached, after applying skin electrodes, thermistor sensor and acceleration transducer. Patients with skin temperature < 32^oc were not considered. Assessment of residual neuromuscular block using Train of Four Ratio and clinical tests were carried out by the anesthesiologist in charge of the recovery room. Clinical tests included assessment of ability to sustain head lift for 5 seconds and ability to cough. Train of four stimulation with the help of Train of Four -Guard neuromuscular monitor, stimulating the ulnar nerve at the wrist was conducted.

Supramaximal electrical stimulation of 30-40 mA was used. Residual neuromuscular block was diagnosed if,

- 1) Less than four responses were obtained after Train of Four stimulation.
- 2) There was fade on Train of Four response.
- 3) The ratio of T₄ - T₁ is <0.80.
- 4) Conscious, awake patients were unable to sustain head lift for 5 seconds and cough on oral command.

In patients in whom response to peripheral nerve stimulation indicated residual neuromuscular block Train of Four Ratio <0.80, Train of Four stimulation was continued and response assessed every minute until Train of Four Ratio reached 0.80. The bedside clinical tests were repeated and time taken to achieve Train of Four Ratio 0.80 was noted.

Skin surface electrodes were used. Low current of 30 -40mA were used for giving electrical stimulation which were tolerated by the patients in immediate post-operative period.

None of the patients showed airway obstruction. No patients with residual neuromuscular block required reintubation or mechanical ventilation in the recovery room.

STATISTICAL ANALYSIS: The data were analyzed by student's t test wherever appropriate, 'p' value <0.05 was considered as statistically significant and 95% confidence interval was calculated for the differences in the parameter between the groups.

Response to ulnar nerve stimulation using T.O.F stimulation

	Group 'P'	%	Group 'A'	%	95% CI for difference between the two percentages
Incidence of R.N.M.B (TOFR <0.80)	20	40	5	10	12.04-47.96

'p' < 0.002 is highly significant

95% confidence interval is 12.04- 47.96.

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The difference in the incidence of neuromuscular block (TOFR <0.80) between the two groups was found to be statistically significant.

Response to bedside clinical tests on arrival in recovery room.

	Group 'P'	%	Group 'A'	%	95 % CI for difference between the two percentages
Able to sustain headlift for 5 sec and cough	25	54.34	39	88.64	14.68 to 53.92

'p' =<0.002 is highly significant

98% confidence interval is 14.68 to 53.92

Applying clinical criteria. only 46 patients in group "P" and 44 patients in group A could be assessed. Others could not be assessed because of drowsiness. The difference in incidence of residual neuromuscular blockade between the two groups was highly significant.

Duration required to attain TOFR of 0.80 in patients with initial TOFR <0.80

		GROUP P	GROUP A
DURATION REQUIRED TO ATTAIN TOFR = 0.80 MINS	MEAN + S.D	9.65+ 5.4413	2.8+ 1.4832
	RANGE	2-19	1-5

'P', 0.0027 IS HIGHLY SIGNIFICANT.

DISCUSSION: The residual neuromuscular block continues to be a significant problem following the use of non-depolarizing muscle relaxants.

Viby Mogensen et.al first reported that the use of non-depolarizing muscle relaxants was followed by postoperative residual paralysis in 42% of the patients even after the administration of reversal agents. Their findings were confirmed by various reports over the years from all over the world.^{2,3}

In our study we found that the incidence of residual neuromuscular block as assessed by TOFR to be 40% and 10% after the use of pancuronium and atracurium respectively.

Restoration of complete skeletal muscle strength is desirable to ensure that patients are able to maintain adequate spontaneous ventilation and a protective airway postoperatively. The pressure of adequate spontaneous ventilation does not guarantee complete reversal of residual neuromuscular block. This is because the diaphragm recovers from the effects of non-depolarizing muscle relaxants more rapidly than the small muscles of the pharynx larynx and the adductor pollicis.¹³

Erikssen et al, found that even at a TOFR of 0.60 at the adductor pollicis, there was pharyngeal muscle dysfunction and an increased risk of aspiration.¹⁴ In clinical practice, the adverse effects of residual neuromuscular block may be increased by the poor cardiopulmonary reserve of the patients and the residual effects of the narcotics, sedatives and inhalational anesthetics used in the intraoperative period.

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Thus, reversal of neuromuscular block must be monitored by observing recovery of muscle power of the small muscles such as the adductor pollicis. A TOFR of 0.70 was generally accepted as an effective indicator of neuromuscular recovery.⁸

P.B. Loan et al, in their study compared TOF-Guard neuromuscular monitor with myography-2000 monitor.¹² They concluded that TOF-Guard monitor provides improvement over simple tactile evaluation in routine neuromuscular monitoring. It is easily setup, simple to use, provides for skin temperature monitoring and has a display of information, which can be stored for later analysis. Hence in our study we employed TOF-Guard neuromuscular monitor for recording. Certain clinical tests have been shown to correlate with TOFR indicating recovery from residual neuromuscular block. Head lift for 5 seconds has been associated with a TOFR of 0.60-0.70.⁸

Jensen Engback et al. concluded that a residual neuromuscular block from atracurium cannot be excluded unless TOFR as measured mechanically or electromyographically has recovered to 0.80.⁹ Hence in our study we defines residual neuromuscular block as TOFR < 0.80. The rate of recovery from non-depolarizing muscle relaxants after their reversal with anticholinesterases is dependent upon their spontaneous rate of recovery and its augmentation by reversal drugs. It was postulated that the more rapid recovery observed after atracurium was a consequence of more rapid spontaneous degradation of the relaxant.⁵

Atracurium, compared with the other intermediate acting non depolarizing muscle relaxants has a shorter duration of action and minimal cumulative and cardiovascular effects. Its termination of action is not dependent on hepatic and renal function. It is inactivated by a self-destructing process known as Hofmann elimination which is dependent on body PH and temperature. Hence recovery from atracurium is rapid and incidence of residual neuromuscular block should be low.¹⁵

We found an incidence of 10% of residual neuromuscular block after the use of atracurium as assessed by Train of Four response, which is lower than incidence observed with pancuronium (40%). Our results are similar to those reported by Bevan and Smith⁴ who carried out the first study comparing residual neuromuscular block after the use of pancuronium, atracurium and vecuronium by tactile and visual assessment of Train of Four and DBS. They found an incidence of residual neuromuscular block of 36%, 4.34%, and 8.7% following the use of pancuronium, atracurium and vecuronium respectively.

One of the limitations of our study is that the anesthesiologist anaesthetizing the case in the operating room was aware that the patient would be monitored for residual neuromuscular block in the recovery room and would therefore be more cautious during the use of the relaxants intraoperatively.

In spite of it, the incidence of residual neuromuscular block in our study is substantial. Another criticism of our study could be that the dose of muscle relaxants was not standardized and the study does not identify the cause of residual neuromuscular block. However the common factor for all the patients was that the anesthesiologist was satisfied that the patient had recovered clinically sufficiently to be extubated and shifted to the recovery room. Such a design has the advantage of making observations relevant to clinical anesthesia.

In the patients who exhibited residual neuromuscular block, mean time to complete recovery i.e., Train of Four Ratio = 0.80 was 9.65 mins for group 'P' and 2.8 mins for group 'A'. Olli and Meretopa who electromyographically recorded Train of Four response found that atracurium had a shorter half time of recovery than the long acting agent pancuronium.¹¹ Whalley and Lewis also used

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Train of Four stimulation at the adductor pollicis but assessed Train of Four Ratio upto 0.70.¹⁶ they reported that the time taken to recover from pancuronium and equipotent doses of atracurium was the same.

G.S. Murphy, has mentioned methods to reduce the risk of residual neuromuscular blockade by use of routine neuromuscular monitoring in operating, acceleromyography monitoring during surgical procedure; avoidance of total twitch separation.¹⁶

A. Butterlyl have mentioned that Post Anesthesia Care Unit length of stay was significantly longer in patients with Train of Four Ratio less than 0.9¹⁷ and also Murphy Glesn S et.al have also concluded that incidence and severity of symptoms of muscle weakness were increased in Post Anesthesia Care Unit with a Train of Four less than 0.9¹⁸

CONCLUSIONS:

- 1) Our study concludes that the incidence of residual neuromuscular block in patients receiving pancuronium and atracurium were 40% and 10% respectively. Thus residual neuromuscular block can be a significant problem in recovery room, during the postoperative period.
- 2) The use of intermediate acting non depolarizing muscle relaxant like atracurium lowers the incidence of residual neuromuscular block but does not eliminate it.
- 3) All patients receiving non depolarizing muscle relaxants should be monitored in the recovery room for at least 40 minutes postoperatively.

REFERENCES:

1. Viby-Mogensen J, Bent CJ, Ording H. Residual curarization in the recovery room. *Anaesthesiology* 1979; 50: 539-541.
2. Beecher HK, Todd DP. A study of the details associated with anaesthesia and surgery. *Ann Surg* 1954; 140(1): 2-34.
3. Cooper AL, Leigh JM, Tring IC. Admissions to the intensive care unit after complications of anesthetic techniques over 10 years. *Anaesthesia* 1989; 44: 953-958.
4. Bevan DR, Smith CE, Donati F. Postoperative neuromuscular blockade: A comparison between Atracurium, Vecuronium and Pancuronium. *Anaesthesiology* 1988; 69: 282-276.
5. Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G. Clinical pharmacology of atracurium besylate (BW33A): A new non-depolarising muscle relaxant. *Anaesthesiology* 1982; 61(9): 723-734.
6. Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarising block. *Br J Anaesth* 1971; 43: 473-485.
7. Ali HH, Kitz RJ. Evaluation of recovery from non-depolarizing neuromuscular block, using a digital neuromuscular transmission analyzer; preliminary report. *Anaesth Analg*, 1973; 52: 740-743.
8. Brand JB, Cullen DJ, Wilson NE, Ali HH. Spontaneous recovery from non-depolarizing neuromuscular blockade: correlation between clinical and evoked responses. *Anaesth Analg* 1977; 56(1): 55-58.
9. Engback J, Ostergaard D, Viby- Mogensen J, Skovgaards LY. Clinical recovery and train of four ratio measured mechanically and electromyographically following atracurium. *Anaesthesiology* 1989; 71: 391- 395.

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10. Hayes AH, Mirakhur RK, Breslin DS, Reid JE, McCourt KC. Postoperative residual block after intermediate acting neuromuscular blocking drugs. *Anaesthesia* 2001; 56: 312-318.
11. Ali HH, Wilson RS, Savarese JJ, Kitz RK. The effects of tubocurarine elicited train of four muscle response and respiratory measurements in humans, *Br J Anaesth* 1975; 47: 570-573.
12. Loan PB, Paxton LD, Mirakhur RK, Connolly FM, McCoy EP. The TOF Guard neuromuscular transmission monitor. A comparison with the Myography 2000. *Anaesthesia* 1995; 50: 699-702.
13. Chusin M, Lebrault C. The neuromuscular blocking effects of vecuronium on human diaphragm. *Anaesth Analg* 1987; 66: 112-117.
14. Erikson LI, Sundman E, Olsson R, Nilsson L, Witt H, Ekberg O. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans. *Anaesthesiology* 1997; 87: 1035-43.
15. Payne JP, Hughes R. Evaluation of atracurium in anesthetized man. *Br J Anaesth* 1981; 53: 45-53.
16. Whalley DG, Lewis B, Becodes NM. Recovery of neuromuscular function after atracurium and pancuronium maintenance of pancuronium block. *Can J Anaesth* 1994; 41: 31-35.
17. G.S.Murphy. Residual neuromuscular blockade, incidence assessment and relevance in the postoperative period. *Minerva Anestesiologica*, 2006 ;(72)97:109.
18. A.Butterlyl et al. Post operative residual curarization from Intermediate acting neuromuscular blocking agents. *BJA*, 2010; 105; 304:309.
19. Murphy, Glenn S et al. Post operative residual neuromuscular blockade is associated with impaired clinical recovery. *Anaesthesia & Analgesia*, 2013 ;(117)1, 133:141.

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