"COST ANALYSIS AND SAFETY COMPARISON OF ATRACURIUM AND CISATRACURIUM IN PATIENT UNDERGOING GENERAL ANESTHESIA"

By

Dr T.V.ARUN KUMAR

Dissertation submitted to

B.L.D.E. (Deemed to be) UNIVERSITY VIJAYAPUR, KARNATAKA

In partial fulfilment of the requirements for the degree of

DOCTOR OF MEDICINE

IN

ANESTHESIOLOGY

Under the guidance of

Dr VIJAYKUMAR T.K

PROFESSOR

DEPARTMENT OF ANESTHESIOLOGY

B.L.D.E. (Deemed to be University)

SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE, VIJAYAPUR

KARNATAKA

2024

DOI 10.5281/zenodo.15501496
https://zenodo.org/records/15501497

DECLARATION BY THE CANDIDATE

I declare that this dissertation entitled "**COST ANALYSIS AND SAFETY COMPARISON OF ATRACURIUM AND CISATRACURIUM IN PATIENT UNDERGOING GENERAL ANESTHESIA**", is a bonafide and genuine research work carried out by me under the guidance of DR. VIJAY KUMAR T.K, Professor, Department of Anesthesiology, Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapura.

DATE:

PLACE:

Dr T.V.ARUN KUMAR
DEPARTMENT OF ANESTHESIOLOGY
B.L.D.E (DEEMED TO BE) UNIVERSITY
SHRI B. M. PATIL MEDICAL COLLEGE
HOSPITAL AND RESEARCH CENTRE,
VIJAYAPUR, KARNATAKA

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled "**COST ANALYSIS AND SAFETY COMPARISON OF ATRACURIUM AND CISATRACURIUM IN PATIENT UNDERGOING GENERAL ANESTHESIA**" is a bonafide research work done by Dr T.V.ARUN KUMAR in partial fulfilment of the requirement for the degree of M.D. in ANESTHESIOLOGY.

DATE:

PLACE:

Dr VIJAY KUMAR.T.K
PROFESSOR
DEPARTMENT OF ANESTHESIOLOGY
B.L.D.E (DEEMED TO BE) UNIVERSITY
SHRI B. M. PATIL MEDICAL COLLEGE
HOSPITAL AND RESEARCH CENTRE,
VIJAYAPUR, KARNATAKA

ENDORSEMENT BY THE HEAD OF DEPARTMENT

This is to certify that the dissertation entitled "**COST ANALYSIS AND SAFETY COMPARISON OF ATRACURIUM AND CISATRACURIUM IN PATIENT UNDERGOING GENERAL ANAESTHESIA**" is a bonafide research work done by Dr T.V.ARUN KUMAR under the guidance of Dr VIJAYKUMAR T.K, Head of the department, Department of Anesthesiology, Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapura.

DATE:

PLACE:

Dr RENUKA HOLYACHI MD

HEAD OF THE DEPARTMENT

DEPARTMENT OF ANESTHESIOLOGY

B.L.D.E (DEEMED TO BE) UNIVERSITY

SHRI B. M. PATIL MEDICAL COLLEGE

HOSPITAL AND RESEARCH CENTRE,

VIJAYAPUR, KARNATAKA

ENDORSEMENT BY THE PRINCIPAL

This is to certify that the dissertation entitled "**COST ANALYSIS AND SAFETY COMPARISON OF ATRACURIUM AND CISATRACURIUM IN PATIENT UNDERGOING GENERAL ANESTHESIA**" is a bonafide research work done by Dr T.V.ARUN KUMAR under the guidance of Dr VIJAYKUMAR .T.K, Head of the department, Department of Anesthesiology, Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapura.

DATE:

PLACE:

Dr ARAVIND PATIL

PRINCIPAL

DEPARTMENT OF ANESTHESIOLOGY

B.L.D.E (DEEMED TO BE) UNIVERSITY

SHRI B. M. PATIL MEDICAL COLLEGE

HOSPITAL AND RESEARCH CENTRE,

VIJAYAPUR, KARNATAKA

COPYRIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that the B. L. D. E. (DEEMED TO BE) UNIVERSITY, SHRI B. M. PATIL MEDICAL COLLEGE AND HOSPITAL RESEARCH CENTRE, VIJAYAPURA, KARNATAKA shall have the rights to preserve, use and disseminate this dissertation/thesis in print or electronic format for academic / research purpose.

DATE:

PLACE:

Dr T.V.ARUN KUMAR
DEPARTMENT OF ANESTHESIOLOGY
B.L.D.E (DEEMED TO BE) UNIVERSITY
SHRI B. M. PATIL MEDICAL COLLEGE
HOSPITAL AND RESEARCH CENTRE,
VIJAYAPUR, KARNATAKA

ACKNOWLEDGEMENT

On completion of my post-graduation journey and this scientific document, I would like to acknowledge the immense help received from my mentors in the department of Anaesthesiology. With privilege and respect, I would like to express my gratitude and indebtedness to my Guide, Dr Vijaykumar T.K Professor, Department of Anaesthesiology and for his constant inspiration, extensive encouragement and loving support, which rendered in pursuit of my post-graduate studies and in preparing this dissertation.

I am forever grateful to Dr Renuka Holyachi MD, Professor and HOD of Department of Anaesthesiology, Shri B.M Patil Medical College, Hospital and Research Centre, Vijayapura for her valuable suggestions, support and encouragement throughout the post graduate programme.

I am grateful to all my teachers in Department of Anaesthesiology for their guidance, encouragement and inspiration.

I am extremely thankful to Professor Dr Aravind Patil, Principal, of B.L.D.E.(DU) Shri. B.M. Patil Medical College, Hospital and Research Centre, Vijayapura, for permitting me to utilize resources in completion of my work.

My thanks to one and all staff of Library, Anaesthesia Department and Hospital for their co-operation in my study I am thankful to the members of ethical committee BLDEU's Shri. B. M. Patil Medical College Hospital and Research Centre Vijayapur for permitting me to carry out this study.

I am thankful to Dr Vijaya Sorganvi for her help in statistical analysis. I also like to thank all my batchmates especially Dr Syed Sufiyan and Dr Reshma & seniors and juniors for their help and co-operation.

I would like to express my deep-felt gratitude to my parents for their constant support and encouragement throughout.

Last but not the least; I convey my heartfelt gratitude to all my patients, without whose co-operation, this study would be incomplete.

Dr T .V. ARUN KUMAR

ABSTRACT

The neuromuscular blocking agent plays an essential role in balanced anaesthesia, and the introduction of skeletal muscle relaxants has revolutionised the field of anaesthesia and critical care. In the operation theatre, skeletal muscle relaxants are used for two purposes: one is to do endotracheal intubation, and another purpose is to give relaxation during surgery. Atracurium and cisatracurium, intermediate acting, benzylisoquinolone Non depolarizing neuromuscular blocking agents, are used for endotracheal intubation when there is a contraindication for succinylcholine. These drugs have fewer side effects, and organ-independent elimination has made it the most commonly used neuromuscular agent. The present study is designed to evaluate the adverse drug reactions and economic benefits of both drugs.

MATERIALS AND METHODS:

This study included 140 patients scheduled to undergo elective surgery under general anaesthesia with endotracheal intubation and required intraoperative neuromuscular blockade. The study subjects were randomly split into two groups of 70 each.

Group A: 70 patients receiving Atracurium 0.5mg/kg

Group B: 70 patients receiving cisatracurium 0.15mg/kg

Atracurium and cisatracurium were given to the patients just before endotracheal intubation and were assessed for adverse drug reactions and cost benefit between both drugs

RESULT

The hemodynamics like MAP, PR, SPO2, ECG, other clinical features, adverse reactions, and the drug's cost were assessed. In terms of side effects, both drugs provide similar safety profiles, and cisatracurium is slightly a safer drug as it does not cause much hemodynamic changes and nil histamine release and can safely used in asthma and other histamine related disorders. In terms of cost comparison, Atracurium has economic benefits than cisatracurium

CONCLUSION

Both drugs have a similar safety profile, and cisatracurium is a better choice for patients with hemodynamic instability and those with a risk of histamine related disorders like asthma and anaphylaxis. In terms of economic benefit, atracurium is a better choice.

KEY WORDS

Atracurium, cisatracurium, adverse effect and cost analysis

TABLE OF CONTENTS

LIST OF GRAPHS

LIST OF TABLES

LIST OF FIGURES

ABBREVATIONS

ASA- American Society of Anaesthesiologists

ECG- Electrocardiogram

HR- Heart rate

BP- Blood Pressure

I.V- Intravenous

Inj - Injection

NIBP- Non-invasive Blood Pressure

SPO2- Oxygen Saturation

S.D- Standard Deviation

PNS-Peripheral Nerve Stimulator

mcg- Microgram

mg- Milligram

kg- Kilogram

mL- Millilitre

hrs- Hours

mins- Minutes

Sec- seconds

P - ‘p’ value

Sl. No.- Serial number

SBP:- Systolic blood pressure

DBP:- Diastolic blood pressure

TOF- Train of four

INR – Indian national rupees

ETT – Endotracheal tube

ETCO2 – End-tidal capnography

CBC – Complete blood cell count

RBS – Random blood sugar

HIV – Human immunovirus

HbsAg – Hepatitis B antigen

BT – Bleeding time

CT – Clotting time

NMBA – Neuro muscular blocking agents

EF –Ejection fraction

ICU –Intensive care unit

OT – Operation theatre

CNS – Central nervous system

ECF – Extracellular fluid

NMJ – Neuro muscular junction

INTRODUCTION

The introduction of skeletal muscle relaxants in 1942 into anaesthetic practice was an important development in the field of anaesthesia and critical care. Non-depolarizing or competitive NMBA differ in pharmacokinetics in terms of onset of action, duration of action, metabolic route, potency, and adverse effect [2, 3.]

Neuromuscular blocking drugs are used in the operation room, and intensive care to provide Skeletal muscle relaxation for their muscle relaxation effects are required to improve oxygenation and ventilation, facilitate intubation, produce immobility during surgery [1], reduce vocal cord tension, minimize response to laryngoscopy, and position the tube in the trachea with minimal effort. Without neuromuscular blocking medications, laryngoscopy is associated with significant difficulties.[4]

Atracurium and Cisatracurium are two competitive NMB agents with intermediate duration of action2

Atracurium is a non depolarizing or competitive neuromuscular blocking agent that was introduced into clinical practice in year 1983. It has an intermediate duration of action and a rapid onset of action—the intubating condition can be reached after two x ED95 doses in two to three minutes, with no dependence on any organ for metabolism or elimination, no cumulative effects, it decomposes into inactive metabolites through ester hydrolysis and hofmann elimination,

which has minimal cardiovascular effects, and can be easily reversed by neostigmine.[5]

While it lacks the cardiovascular effects and histamine-releasing qualities of atracurium, cisatracurium, another non-depolarizing skeletal muscle relaxant, was released in 1995 and is five times more effective than atracurium in other respects [6,7.] Cisatracurium is a benzylisoquinolinium non depolarizing neuromuscular blocking agent of intermediate duration. With a potency of three to four times that of atracurium, it is a stereoisomer of atracurium. Even at doses as high as 0.4 mg/kg (8×ED95), cisatracurium does not produce histamine and is linked to more stable hemodynamics than atracurium, despite its greater potency. [8,9]

Both drugs have been compared in bolus and injection forms10. Both these drugs have been studied and compared for effective cost analysis and to prove which drug has a safety profile .cisatracurium is associated with a lower potency to cause histamine release and has a longer onset time at equal doses when compared with atracurium [11]

AIMS AND OBJECTIVE

To study the adverse reaction, safety and cost effective analysis between the cis atracurium and atracurium in patients undergoing general anaesthesia

PRIMARY OBJECTIVE:

To study the safety profile and adverse drug reaction prevalence between cisatracurium and atracurium in patients undergoing general anaesthesia

SECONDARY OBJECTIVE:

To study the cost analysis between cisatracurium and atracurium in patients undergoing general anaesthesia

REVIEW OF LITERATURE

Masoud Ghorbanlo et al. (24), in 2016, conducted a prospective randomised double blinded study on Cisatracurium and Atracurium in patients with low function of left ventricle whose EF is 35 and lesser for open heart surgery. The patients were randomly divided into two groups of 30 patients each. All patients received midazolam, etomidate, and one of the muscle relaxants under consideration—0.2 mg/kg of cisatracurium or 0.5 mg/kg of atracurium—within a minute of the induction stage. The same muscle relaxants used in the induction stage of anaesthesia, midazolam and sufentanil, were infused into the patients during the maintenance phase. There was no statistically significant difference between the two groups with regard to descriptive indexes such as age and sex distributions, premedication with cardiac medications, ejection fraction before surgery, and fundamental disease. The conclusion was that the two study groups' hemodynamic indices differed significantly and that patients who are posted for open heart surgery and have poor left ventricular function require hemodynamic stability throughout the entire surgical process. This indicates that using cisatracurium as a muscle relaxant is advantageous and more beneficial.

Dr Mitali Khobragade N et al. (25), 2020 did a prospective randomised double blind study comparing the effects of cisatracurium with atracurium for intubating conditions during general anesthesia. In this study, two groups of thirty patients

each were randomly assigned. For intubation, Group B received cisatracurium 0.15 mg/kg, and Group A received injectable atracurium 0.5 mg/kg. Laryngoscopic grading, the number of intubation attempts, the duration of the procedure, hemodynamic parameters, and histamine release indicators were recorded. It was discovered that the laryngoscopic grading in 50% of Group A patients and 100% of Group B patients was grade I, or excellent, and grade II, or good, in 50% of Group A patients. In both groups, each patient was intubated on their first attempt. Intubation time was statistically significant. The two groups' hemodynamic parameters were similar. Since histamine release was not observed in any of the groups, it was determined that atracurium and cisatracurium were equivalent under intubating circumstances.

.

Dr PD Subha et al. 26, 2019, conducted a prospective randomised single, blinded comparative study on the effectiveness of cisatracurium and atracurium in general anesthesia. 156 patients were systematically categorised into two groups, Group A (atracurium) and Group B (cisatracurium), each with 78 patients. Vital parameters, intubation score, and the length of the patient's procedure were all recorded. The average onset time, duration of action, and recovery time for Cisatracurium patients were found to be 165.95 seconds, 57.41 minutes, and 121.62 minutes, respectively. Atracurium patients in the same group also exhibited mean onset times of 196.95 seconds, 34.58 minutes for duration of action, and 150.65 minutes for recovery. The average jaw relaxation, vocal cord,

intubation response, and mean intubating scores for Cisatracurium individuals were 2.90, 2.77, 2.85, and 2.90, respectively.

Alisha Sahu27 et al.,2020 conducted a prospective, double-blind, randomised trial to compare the effectiveness of atracurium and cisatracurium in patients having retrograde cholangiopancreatography procedures while sedated. In this study, 100 adult patients, both male and female, between the ages of 18 and 60, who were listed for ERCP procedures under general anesthesia and fell into the American Society of Anaesthesiologists I/II category, were randomly divided into two groups of 50. Intravenous injections of atracurium (0.5 mg/kg) and cisatracurium (0.2 mg/kg) were administered to Group A and Group B, respectively. The length of action, time to maximum blockade, intubating condition, intubation time, hemodynamic parameters during intubation, and after 1, 2, 3, 5, and 15 minutes, as well as any adverse effects, were observed. The condition of intubation was found to be enhanced.

Dr Jyoti Kale28 et al. 2020, evaluated the onset, duration of action, and intubating conditions of atracurium and cisatracurium in a randomised controlled clinical trial. Two groups of patients, Group A (atracurium) and Group B (cisatracurium), were formed. atracurium (2×ED95 dose; 0.5 mg/kg) was given to group A, while cisatracurium (4×ED95 dose; 0.2 mg/kg) was given to group C. Using a Train-of-Four monitor, endotracheal intubation was performed at a

TOF score of 0. The study showed no statistically significant variation in the mean Intubating condition score. Group A's mean onset time was 3.7 minutes, which was faster than Group C's 6.04 minutes, compared to Group C, whose mean duration of action was 59.43 minutes, which was noticeably longer than Group A. 38.93 minutes came to the conclusion that both medications provide similar intubating conditions. Atracurium 2×ED95 dose has a faster onset & shorter duration of muscle relaxation than Cisatracurium 4×ED95 dose.

Dr Pranathi29 et al.,2019, conducted a prospective, randomised, single-blinded study between June 2018 and May 2019 to compare the onset, duration, and intubating conditions of atracurium and cisatracurium during general anesthesia. The study was conducted on 60 patients, divided into three groups: Group A received atracurium (0.5 mg), Group B received 0.1 mg, and Group C received 0.15 mg of the respective drug. The results showed that there was no significant difference ($p>0.05$) between Group 1 and Group C in terms of vocal cord position, jaw relaxation, and response to intubation. After 5 minutes, the heart rate, SBP, and DBP gradually returned to baseline; this would possibly have been the result of a response to stress and was not statistically significant. And was concluded that, when compared to cisatracurium 0.1 mg/kg and atracurium 0.5 mg/kg, cisatracurium 0.15 mg/kg provides excellent intubating conditions with a rapid onset of action, a longer duration of action, and no significant

hemodynamic changes. As a result, cisatracurium 0.15 mg/kg can be used as the optimal non-depolarising muscle relaxant for intubation.

In the year 2021, **Dr Usha Badole30 et al.,** in a study of 60 ASA I and II patients undergoing elective abdominal surgery under general anaesthesia, were participants in a prospective, randomised comparison study that compared the effects of cisatracurium and atracurium. Patients were randomly divided into two equal groups. Group C received 0.3 mg/kg of cisatracurium, while Group A received 0.5 mg/kg of atracurium. All patients received standardised GA in the following manner: if the intubating condition was satisfactory (good or outstanding), intubation was performed; if it was poor or inadequate, it was attempted again every 30 seconds by the anaesthesiologist who was blind to the provided NMB. Heart rate, intubation conditions, and mean arterial blood pressure (MAP) were measured. The TOF count was interpreted in terms of the recovery index, clinical duration, and start of action. After 120 seconds, cisatracurium (85%) was more common than atracurium (0%), and after 180 seconds, cisatracurium (100%) and atracurium (80%) were more common than atracurium (0%), leading to clinically acceptable intubating conditions. Atracurium exhibited a significantly longer duration of action than cisatracurium (30±5 versus 60±5min), whereas cisatracurium had a significantly faster onset (120±30 versus 180±30sec). There was no evidence of any significant clinical cardiovascular changes in both groups. They came to the conclusion that both

atracurium and cisatracurium are powerful, safe, and have great cardiovascular stability. Atracurium has an intermediate duration of action, while cisatracurium has a rapid onset of action with suitable intubating circumstances.

In the year 2023, **Dr. Ashwin Sharma31 et al**, in a study of 60 patients between the ages of 20 and 65 who had physical status classified as ASA grades 1 and 2, posted for elective surgeries under GA, participated in a randomised controlled trial study to evaluate the intubating conditions with two different doses of cisatracurium (0.15 mg/kg and 0.20 mg/kg) in terms of onset time, intubating conditions, untoward effects, and hemodynamic response. Applying clinical assessment and the train of four fading. Patients were split into two groups of 30 each at random. Group B received 0.2 mg/kg of cisatracurium, while Group A received 0.15 mg/kg. Thirty patients in each group were compared for intubation. This study indicated that group B, which received cisatracurium at a dose of 0.15 mg/kg, had improved intubating conditions and a mean time between intubating dose and the first maintenance dose.

In 2022, **Siril Pati32 et al.** conducted a prospective randomised control study on 60 people to compare the recovery profiles of patients undergoing lengthy procedures implementing a train of four between the continuous infusion of cisatracurium and the repeated bolus dose. In this trial, patients were randomly assigned to receive either an infusion of cisatracurium that is started and titrated

to maintain a 90%–95% neuromuscular blockade or 0.02 mg/kg IV repeat bolus doses (Group B). (Group C). Group B and Group C consumed an average of 22.30 mg and 36.03 mg of medication, respectively. Group B and Group C also had mean times to train of four (TOF) ratios of 0.8, 33.57 min and 45.50 min, respectively. They came to the conclusion that using an intermittent bolus dosage of cisatracurium is preferable to an infusion for long procedures. This favours lower intraoperative drug dose and shorter recovery time postoperatively.

In 2019, **Adel Amen Hama33 et al.** conducted a study to compare the effect of blood pressure change between Rocuronium and Atracurium during General Anaesthesia. Fifty adult patients were divided into two groups: the rocuronium 25 patients, and the atracurium group, 25 patients, ages ranging from (18-60 years) of both sexes who were (ASAI and ASAII) patients undergoing (elective surgeries) . Using an intravenous dose of propofol (1.5–2.5 mg/kg), ketamine (0.5 mg/kg), or propofol (2–3 mg/kg), anesthesia was achieved. For maintenance, rocuronium(0.1-0.2 mg/kg) or atracurium drug (0.5 mg/kg)was used for endotracheal intubation. Blood pressure and MAP were measured for 60 seconds, five minutes, and then every five minutes for 15 minutes. P-value of MAP at pre-operative for both the drug groups using rocuronium and atracurium was 0.811, which was insignificant. It was 0.309 at induction, which was not statistically significant. It was 0.574 after one minute, meaning it was not significant. After 5 minutes, the insignificant value was 0.321. It was 0.954 after

10 minutes, indicating it was not significant. Under general anesthesia, the effects of rocuronium and atracurium drugs on blood pressure vary. The atracurium drug alters MAP less significantly. While it might not matter in healthy individuals, patients who already have heart disease, brain illness, hypertension, or are elderly may find it unnecessary, as rocuronium medication significantly alters MAP. Patients with pre-existing heart or brain pathology, the elderly, or those with hypertension may use this with caution. In conclusion, the MAP was increased at the induction of the rocuronium drug and was decreased at the induction of the atracurium drug in this study.

TOPICS SPECIFIC TO STUDY

BASICS OF GENERAL ANAESTHESIA

The aim of general anesthesia is to inhibit the autonomic reflexes while keeping the patient unconscious and unable to experience pain. Anaesthetic agents are classified into five primary classes: synthetic opioids, inhalational maintenance medicines, intravenous (IV) induction agents, and neuromuscular blocking medications. [12]

The four major components of balanced (general) anaesthesia are

1. Amnesia
2. Analgesia
3. Muscle relaxation
4. Loss of reflexes

The anaesthetic agents providing balanced anaesthesia are as follows

INDUCTION AGENT

General anaesthesia (GA) is achieved by intravenous induction agents and maintenance of GA is done by inhalational agents. The level of unconsciousness resulting from IV induction drugs varies based on the dosage and administration rate. Awakening results from the brain's redistribution to the muscles, fat, and metabolism.[12]

INHALATIONAL AGENTS

Inhalational anaesthetics are used to maintain anaesthesia. These agents are basically in liquid form, and they are converted into vapour form by special equipment called vaporiser and are absorbed in the alveoli, enter the bloodstream and, reach the brain (the target organ) and cause amnesia and unconsciousness.[12] Inhalational agents also possess the property of muscle relaxation and are poor analgesics.

INTRAVENOUS SEDATIVES

Benzodiazepine drugs are routinely used as a premedication for general anaesthesia and anxiolytics for patients undergoing regional anesthesia.[12] other agents that are used are alpha two blockers like dexmedetomidine for conscious sedation in OT and ICU

SYNTHETIC OPIOIDS

Synthetic opioids are routinely used for its analgesic effect. All opioids can cause respiratory depression, nausea, vomiting, constipation, pruritis and chest wall rigidity as adverse effects.

NEUROMUSCULAR BLOCKING DRUGS

Skeletal muscle relaxants are employed as a part of balanced GA to produce skeletal muscle paralysis and loss of reflexes and also to facilitate intubation. Two categories exist for these: non-competitive (depolarising) and competitive (non-depolarising).

Rapid sequence induction and intubating conditions that are reached in less than a minute are frequently obtained with succinylcholine, a non-competitive NMBD that binds firmly to the receptor site and imitates the effects of acetylcholine.

.

At the neuromuscular junction, competitive NMBDs bind to nicotinic receptors and compete with acetylcholine. These medications include pancuronium, vecuronium, rocuronium, atracurium, and cisatracurium. The duration of action varies from 30 to 40 minutes based on the medicine and dose administered, and the intubating condition can be reached in 1 to 3 minutes.[13]

PHYSIOLOGY OF NEUROMUSCULAR JUNCTION14

Skeletal muscles are connected to the CNS by motor neurons, whose cell bodies are found in the spinal cord. The motor neurons' axons carry impulses from the central nervous system (CNS) to the spinal cord and then to muscle fibres. Acetylcholine is produced by the presynaptic region and released into the synapse, which is located at the terminal regions of the axon. The synaptic cleft is a space between the endplate of the muscle fibres and the synapse and measures about 50 nm in width.

The two parts of the neuromuscular junction are:

One end is by the nerve ending, which forms the presynaptic portion of the neuromuscular junction, and the other end is by muscle fibres, which form the postsynaptic portion. Between these two junctions, a specialised region is called the synaptic cleft.

As the motor nerve ending reaches the NMJ, the nerve terminal gradually loses its myelin coating and almost no myelin sheet at the neuromuscular junction and is isolated from the fluid around it by one or more Schwann cells. The presynaptic membrane is layered to produce active zones as it becomes thicker. Acetylcholine-containing vesicles are grouped up against these active zones. Additionally, voltage-gated calcium channels are arranged alongside these active zones. The Voltage-gated calcium channel gets activated as the action potential nerve impulse reaches the nerve terminal, causing calcium ion influx, and the Acetylcholine molecules are released into the synaptic cleft as a result of calcium ions' attractive pressure on the vesicles grouped in zone 1. The acetylcholine molecules are delivered in the form of quanta. By elevating calcium levels intracellularly, the frequency of these Qantas can be increased. In zone 2, large vesicles are present in the form of a reserve pool. These vesicles are produced when the nerve is repeatedly stimulated, raising the amount of acetylcholine that is needed for impulse transmission.

Acetylcholine receptors are present at the nerve terminal or the presynaptic Ach receptor.

SYNAPTIC CLEFT

It is a gap present in between presynaptic and postsynaptic membrane. It is 20 to 30 nanometres in length, and it is otherwise called a junctional cleft. It is made up of a thin layer of reticular fibres that are filled with ECF. These fibres help in holding the terminals of muscular nerves together firmly.

When the action potential reaches the axon into the nerve terminal, acetylcholine is released from the presynaptic nerve ends. Choline acetyltransferase is used to create acetylcholine from choline and acetate, it is then stored in the terminal's vesicles. Each 45-nanometre-long vesicle contains around five thousand to ten thousand acetylcholine molecules. Acetylcholine is released in the form of quanta, and each quantum corresponds to a single vesicle's contents. Two hundred to four hundred quanta, or 1 to 4 million acetylcholine molecules, are released into the synaptic cleft during an action potential. The calcium ions are important for the binding of vesicles, their fusion, and the release of acetylcholine.

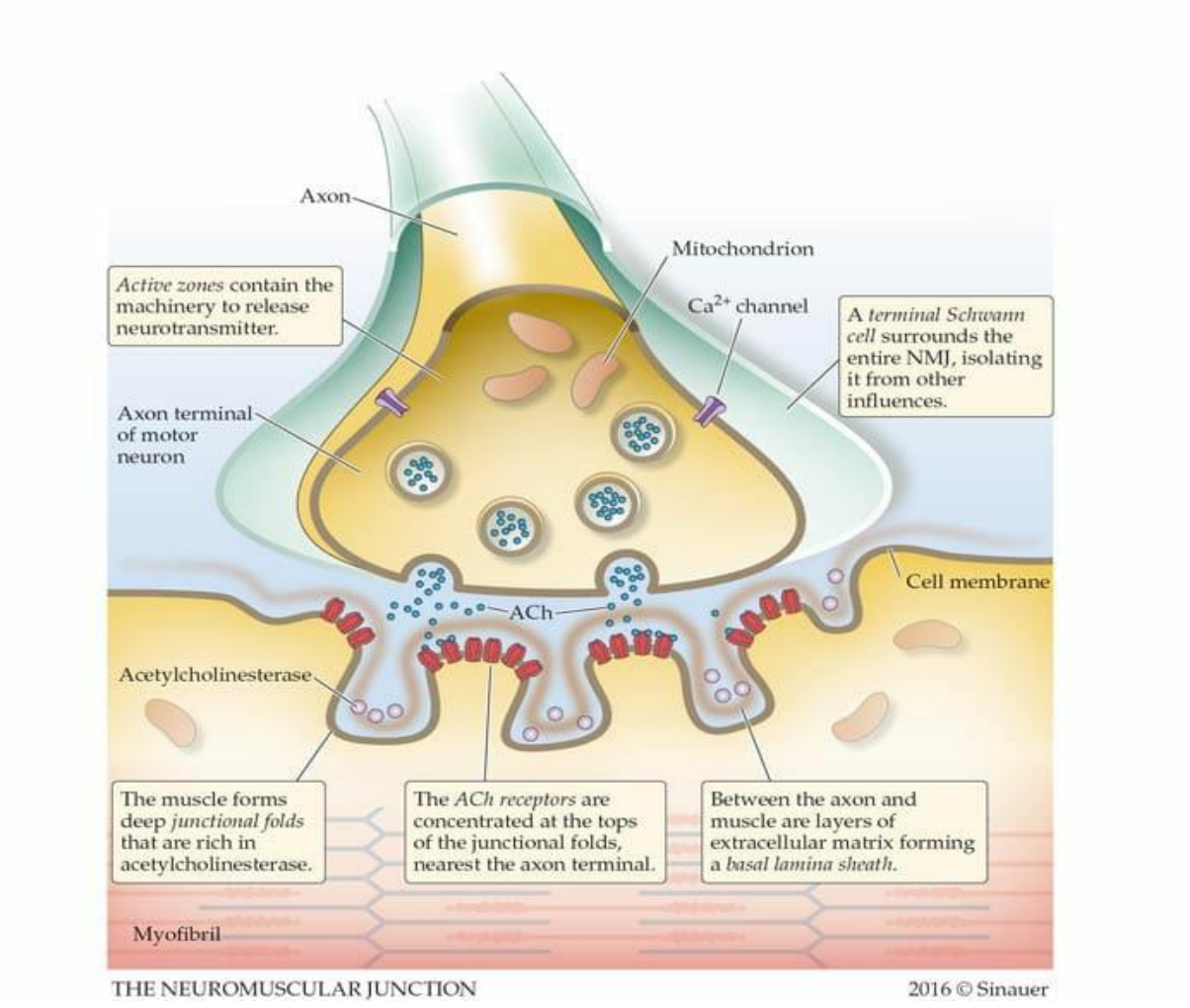


FIG No.1 ANATOMY OF NEUROMUSCULAR JUNCTION

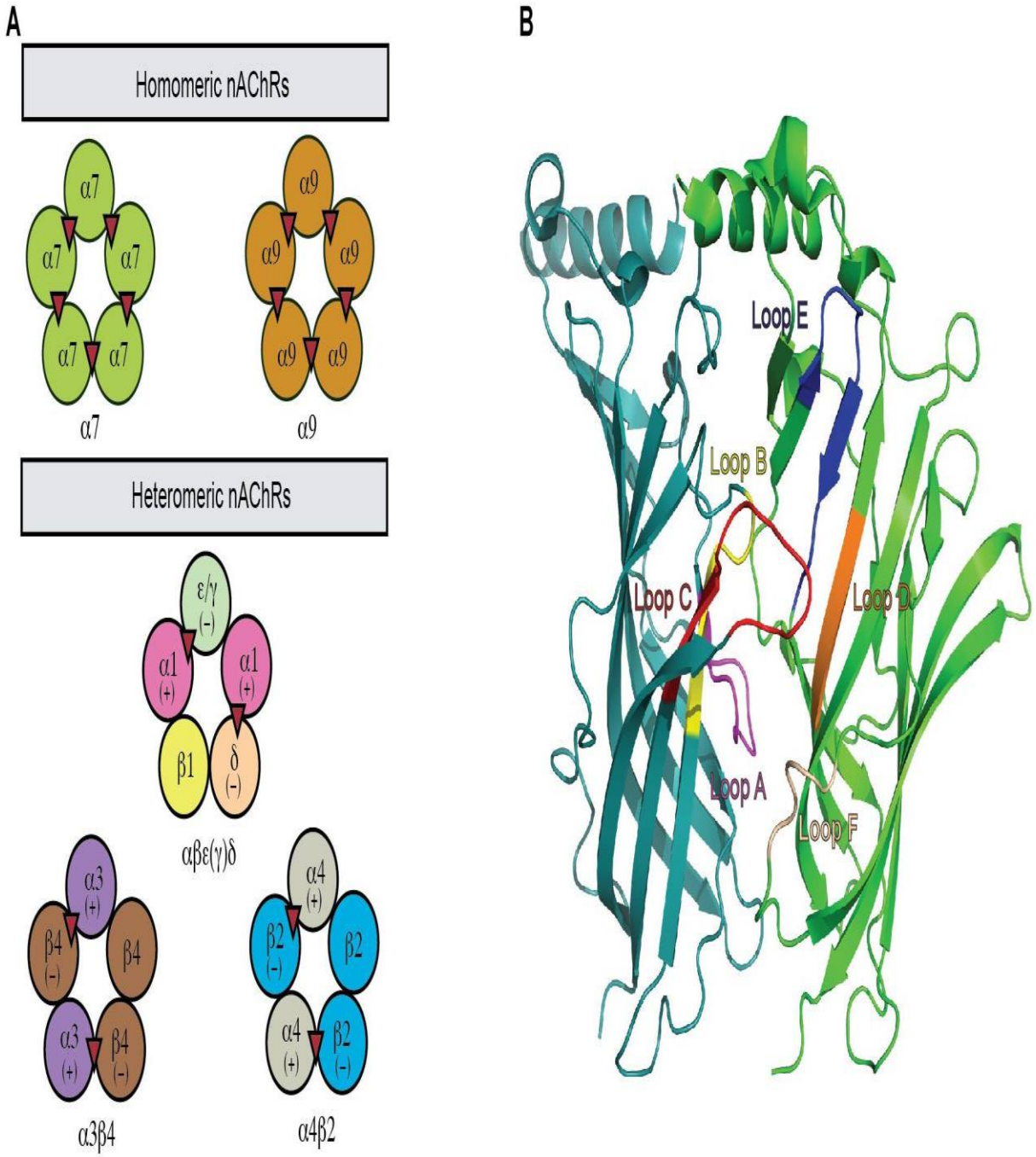


FIG 2: NICOTINIC ACETYLCHOLINE RECEPTOR

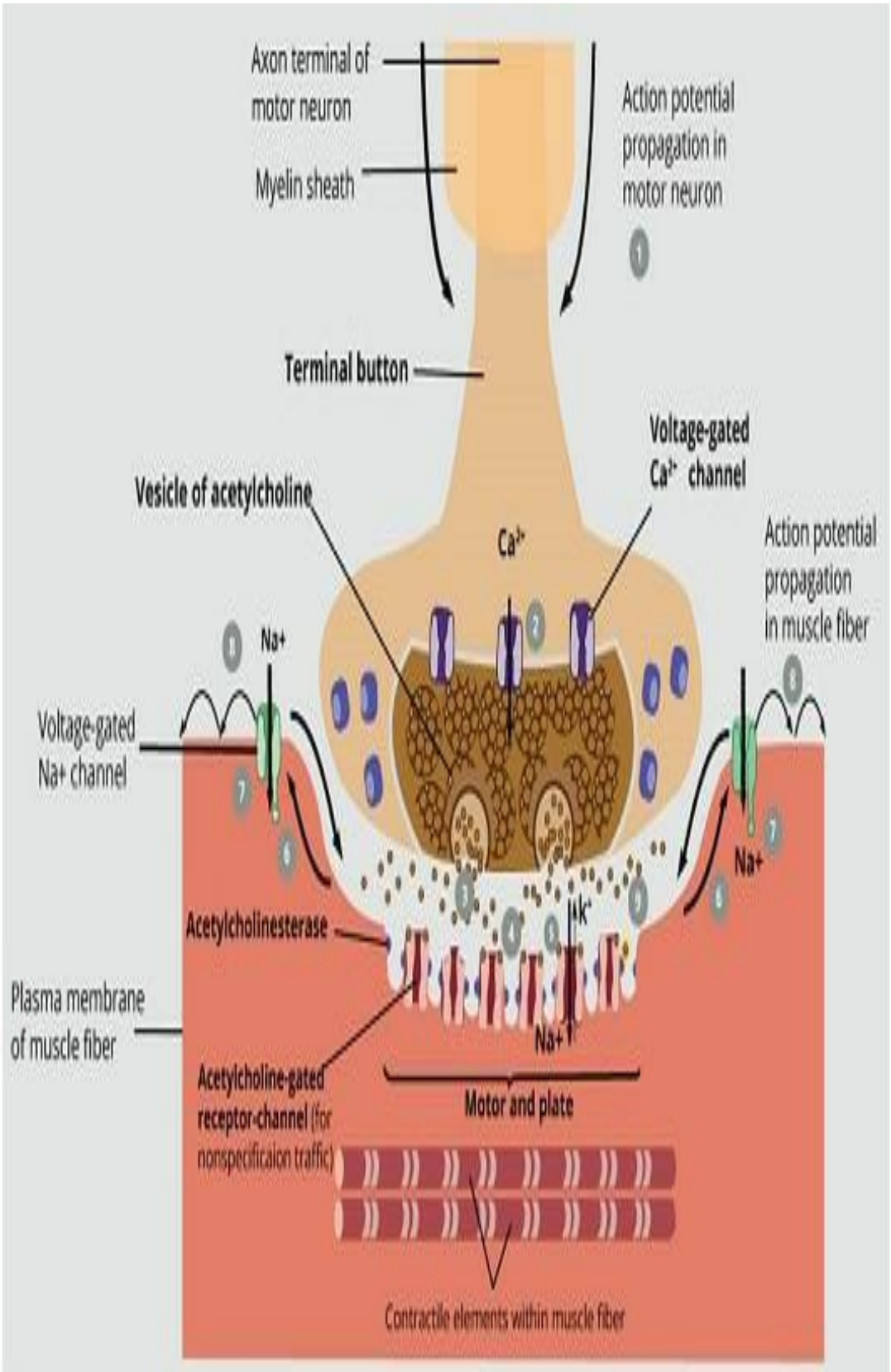


FIG No. 3 PHYSIOLOGY OF NEUROMUSCULAR JUNCTION

Postsynaptic modifications[14,15]

The Muscular endplates are made of nicotinic receptors. These receptors are present around the cellular membrane and are made of 5 glycoprotein subunits, which are arranged in the form of a rosette. The two identical α nicotine subunits and three additional β δ and ε subunits make up the nicotinic subtype at the neuromuscular junction. Acetylcholine binding sites are located outside of the two subunits. A hole forms in the centre of the rosette when two acetylcholine molecules attach simultaneously to each binding site, allowing cations like sodium and potassium to migrate along concentration gradients.

Because of the negative voltage inside the cell, the actual alteration is the movement of sodium ions into the cell. This results in the endplate's inner portion being less negative, which results in depolarization. The prejunctional region and the folds of the synaptic cleft contain a high density of sodium channels, which will open when the membrane depolarization reaches a critical point and further depolarize the cell by allowing sodium influx. Through the activation of the sodium channels, this depolarization generated an action potential that travelled the whole length of the muscle fibre.

PHARMACOLOGY OF NEUROMUSCULAR BLOCKING DRUGS[15]

The primary mechanism of action of the skeletal muscle relaxant is to block the nerve impulse transmission at the neuromuscular junction, which results in muscle paralysis and immobility of the patient intraoperatively. These agents are

classified into non-competitive or depolarizing neuromuscular blocking drugs (succinylcholine) and non-depolarizing or competitive (curare) neuromuscular blocking agents. Based on their mechanisms of action.

Competitive skeletal muscle relaxants are classified based on their duration of action and chemical structure.

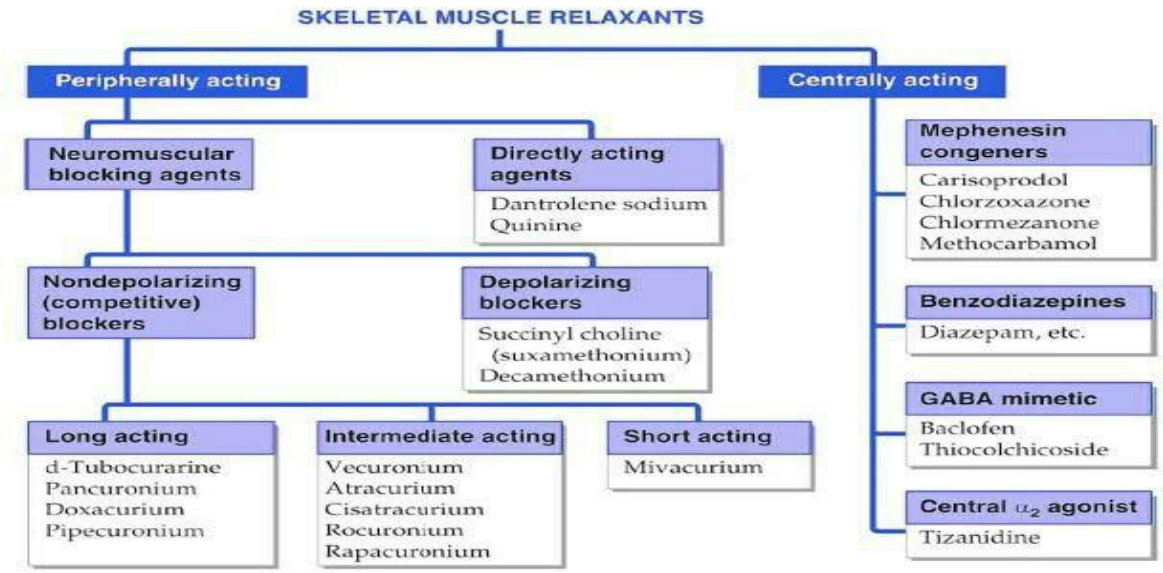


FIG No. 4 CLASSIFICATION OF SKELETAL MUSCLE RELAXANT

CHEMISTRY: NON-DEPOLARIZING BLOCKERS

- Non-depolarizing blocking drugs are classified according to their chemical structure into benzylisoquinolines and ammonio steroids.

Benzylisoquinolines	Ammonio steroids
Tubocurarine	Pancuronium
Atracurium	Pipecuronium
Cisatracurium	Rocuronium
Doxacurium	Vecuronium
Mivacurium	

FIG No. 5 CLASSIFICATION OF NON DEPOLARISING NMBA

Mechanism of action of non-depolarizing neuromuscular blockading

Drugs: Non depolarising or competitive neuromuscular blocking agents act by interacting with nicotinic acetylcholine receptors at the neuromuscular junction without any action on the ion receptor channels to block neuromuscular junction activity. Without causing a change in the structure of those receptors, they compete with acetylcholine for binding to the subunit of the post junctional nicotinic acetylcholine receptors. However, the movements on the post junctional

sites are highly essential. Non depolarising neuromuscular blocking medicines also operate on the pre junctional nicotinic acetylcholine receptors.

Non-depolarising neuromuscular blockade characteristics 16-18

Characteristic responses of skeletal muscle to electrical stimulation by the peripheral nerve stimulator in the presence of non-depolarising neuromuscular blocked include:

a) Reduction in twitching reaction to a single stimulus

b) Unstained response under continuous stimulation (fade)

c) Post tetanic potentiation

d) Other non-depolarising neuromuscular blocking medications are potentiated

e) Conflict brought on by anticholinesterase medications

Drugs that potentate the action of non-depolarising neuromuscular blocking drugs.

These include:

1. Antibiotics like aminoglycosides
2. Nebulised anaesthetics medications
3. Diuretics
4. Regional anaesthetics
5. Magnesium
6. Lithium

ATRACURIUM [19, 20]

Atracurium is a competitive or non-depolarising, intermediate-acting bis quaternary benzylisoquinoline neuromuscular blocking agent. The major sites of action of atracurium are pre and post synaptic cholinergic receptors of the neuromuscular junction. The onset of action is 3 to 5 minutes after administration, and its action lasts 20 to 35 minutes. Its ED95 is 0.2 mg/kg. (21). The intubating dose is 0.5mg/kg, and the maintenance dose is 0.1 mg/kg to 0.2 mg/kg. It produces the release of histamine, which may cause hypotension, tachycardia, and cutaneous flushing.

At normal physiological temperature and pH, atracurium spontaneously undergoes degradation under non-enzymatic process known as Hofmann elimination. Ester Hydrolysis by universal plasma esterases is a second pathway of metabolism that takes place simultaneously. These two pathways of metabolism are organ-independent and unaffected by renal and hepatic dysfunction. As a result, both healthy individuals and those with impaired renal or hepatic function experience the same length of atracurium-triggered neuromuscular blockade. The best metabolite of atracurium's two metabolic routes is laudanosine. About 70% of laudanosine's excretion in the bile and the remaining percentage in the urine are dependent on the liver for clearance.

PHARMACOLOGY OF ATRACURIUM[2]

The molecule of atracurium is a racemic mixture of ten stereoisomers.

EXCRETION & METABOLISM:

Only less than 10% of the drug is excreted unchanged via the biliary and renal routes, which shows that its pharmacokinetics are independent of renal and hepatic routes. The major metabolism is by two different pathways.

HYDROLYSIS OF AN ESTER

This action is catalysed by non-specific esterase

HOFMANN'S ELEMINATION**:**

Spontaneous non-enzymatic chemical degradation of atracurium at physiological pH and temperature results in the formation of 2 major end products as: acrylate and laudanosine.

DOSAGE:

Atracurium is a clear colourless solution containing 10 mg/mL of atracurium, which is available in 2.5ml and contains 25mg of atracurium. The onset of action is 3 to 5 minutes after administration, and its action lasts 20 to 35 minutes. Its ED95 is 0.2 mg/kg.(21). Intubating dose is 0.5mg/kg and 0.1 mg/kg to 0.2 mg/kg is the maintenance dose

STORAGE:

It should be stored between 2 and 8 degrees Celsius because opening it to room temperature causes it to lose 5% to 10% of its potency per month. If it is stored

at room temperature, it should be used in 2 weeks, should not be frozen, and should not be exposed to light.

ADVERSE EFFECTS AND CLINICAL FACTORS:[22]

When the dose of atracurium is given above 0.5 mg/kg, it causes a dose related histamine and causing significant side effects.

TACHYCARDIA AND HYPOTENSION

The cardiovascular side effects occur significantly only when the dose is above 0.5 mg/kg. A transient reduction in systemic vascular resistance is another effect of atracurium. This can be overcome by injecting the drug at a slow rate over 5 to 10 minutes.

BRONCHOSPASM:

Atracurium is usually avoided in patients with bronchial asthma and other respiratory illnesses. Patients with a history of asthma are likely to have severe bronchospasm.

TOXICITY OF LAUDANOSINE:

Laudanosin is a breakdown end product of atracurium produced via Hofmann elimination, which is associated with the central nervous system (CNS) and can cause an increase in the minimum alveolar concentration (MAC) or possibly the onset of seizures. Laudanosine toxicity often only occurs when a patient has received a significantly higher dose or has liver failure. The liver converts laudanosine into bile and urine for excretion.

TEMPERATURE AND PH SENSITIVITY**:**

Hypothermia and acidity usually prolong the duration of atracurium in the neuromuscular junction and in plasma.

INCOMPATIBILITY:

Atracurium gets precipitated as a free acid if it is added straight into a line with an alkaline solution, such as thiopentone sodium**.**

IMMUNE REACTIONS**:**

Rare anaphylactoid reactions caused by atracurium were hypothesised. The most plausible routes are acrylate-mediated immune activation and direct immunogenicity. There have been reports of IgE-mediated antibody reactions to medicines that replace ammonium, particularly treatments that limit neuromuscular activity.

FIG No.6 AMPULE SHOWING INJECTION ATRACURIUM

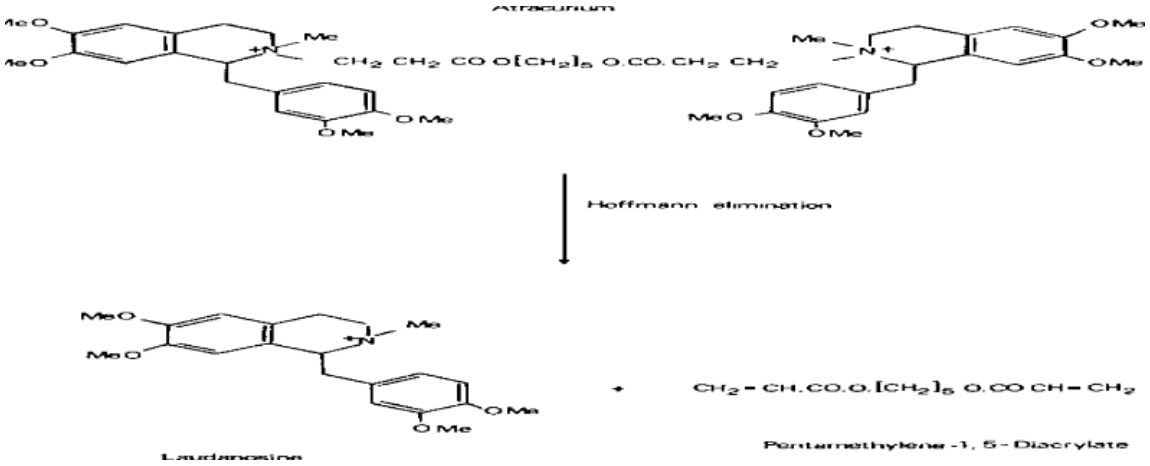
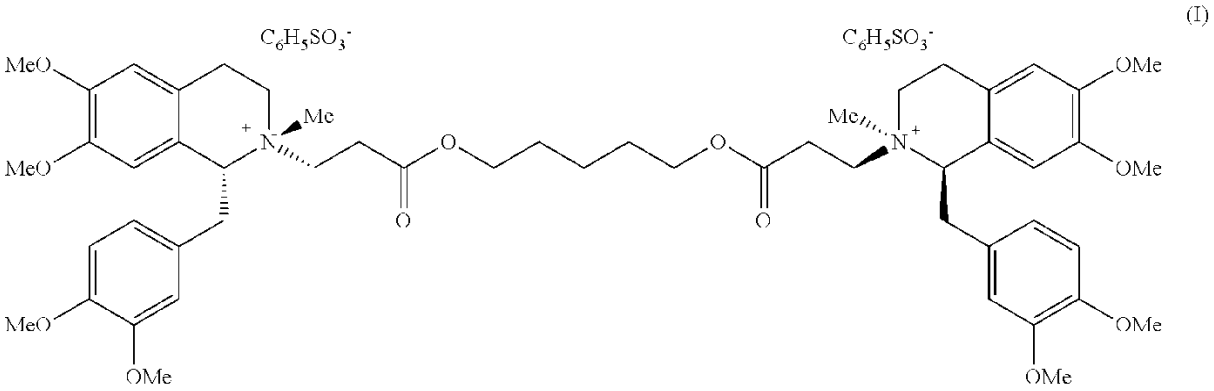


Fig No.8 MOLECULAR STRUCTURE OF ATRACUTIUM AND LAUDANOSIN

CISATRACURIUM[23]



Cisatracurium besylate

FIG. 9 MOLECULAR STRUCTURE OF CISATRACURIUM

Cisatracurium is a competitive skeletal muscle relaxant with an intermediate half-life. It is three times more effective than the isomers of the parent drug and is an R'-cis isomer of atracurium. In young adults receiving N2O/O2 coupled with opioid analgesia, the ED95 of cisatracurium (the dose necessary to achieve 95% suppression of twitch response to nerve stimulation) is 0.05 mg/kg. Similar to atracurium, cisatracurium also degrades spontaneously during metabolism. Even at eight times ED95, cisatracurium does not cause dose-related histamine release and exhibits cardiovascular stability in both healthy individuals and those with IHD.

PHARMACOKINETIC PROPERTIES

Cisatracurium undergoes temperature and pH-dependent chemical degradation by Hofmann elimination. This is the primary route of elimination and accounts for 77% of its total metabolism. Cisatracurium is metabolised to form laudanosine and the corresponding mono quaternary acryl but at a much lower level when

compared with the atracurium. However the renal and hepatic routes of excretion play only a small role in elimination. The liver and kidney play an important route in the elimination of laudanosine.

The volume of distribution of cisatracurium is 0.11 to 0.16 L/kg in normal adult. Cisatracurium is eliminated from the body at a rate of 0.27 to 0.34 L/h/kg, with an elimination half-life of 22 to 35 minutes.

CLINICAL POTENTIAL

A Good intubating condition is achieved after 120 seconds in 90 to 100% of patients receiving cisatracurium 0.15 mg/kg (3 × ED95). (With atracurium 0.5 mg/kg (2 × ED95) after 120 seconds).

The average infusion rate of cisatracurium required to maintain approximately 95% of the block in adult patients undergoing elective surgery ranged between 1.2 and 1.5 µg/kg/min while under N2O/O2/opioid or propofol anesthesia. In two investigations, the mean infusion requirements for children (ages 2 to 12) were found to be 1.6 and 1.8 µg/kg/min..

DOSAGE AND ADMINISTRATION

In a normal healthy adult, cisatracurium 0.15 or 0.2 mg/kg following induction with propofol/N2O/O2 provides excellent intubating conditions within 2 and 1.5 minutes respectively. When given to children (ages 2 to 12), the starting dose is 0.1 mg/kg when combined with either halothane or an opioid. Alongside any

muscle relaxant, dosages should be individualised for each patient, and neuromuscular function is essential to monitor when the drug is administered. Maintenance dosages of 0.03 mg/kg of cisatracurium are administered every 20 minutes (about) for lengthy surgeries. In order to maintain 89 to 99% block during opioid/N2O/O2 anaesthesia, an initial infusion rate of 3 µg/kg/min is administered for continuous infusion, followed by a rate of 1 to 2 µg/kg/min.

FIG.10 CISATRACURIUM 20mg VIAL

MATERIALS AND METHODS

SOURCE OF DATA:

This study was done in the Department of Anaesthesiology, Shri. B.M. Patil Medical College, Hospital and Research Centre, BLDE (Deemed to be University), Vijayapura.

METHOD OF COLLECTION OF DATA:

Study Design: A prospective randomized comparative study

Study Period: One and half years from January 2023 to June 2024

STUDY POPULATION:

This study was done on in-patients undergoing various elective surgical procedures (ASA I and II) under general anaesthesia. On randomly selected 140 adult patients (within 17–80 years) patients of either sex, duration of surgery <2 h.

SAMPLE SIZE: 140 patients

INCLUSION CRITERIA:

a. Patients with age >17 years and <80 years

b. Patients posted for elective surgeries under general anaesthesia (ASA I and II)

c. Both male and female patients

d. Surgery duration less than 2 hours

EXCLUSION CRITERIA:

A. Known hypersensitivity to atracurium and cisatracurium

After obtaining written informed consent and approval from the institutional ethical clearance committee, 140 patients who were scheduled to undergo elective surgery under general anaesthesia with endotracheal intubation and required intraoperative non depolarising neuromuscular blockers were included in the trial. The 140 patients who were a part of the trial were randomly split into two groups.

Group A: 70 patients receiving Atracurium 0.5mg/kg

Group B: 70 patients receiving 0.15 mg/kg

METHODOLOGY

Pre anaesthetic evaluation includes the following:

HISTORY:

· History of underlying medical illness, surgical history, anaesthetic exposure and hospitalization history were elicited.

PHYSICAL EXAMINATION:

· General condition of the patient

· Vital signs -heart rate, blood pressure, respiratory rate

· Height and weight

· Examination of the respiratory system, cardio vascular system, central nervous system and the vertebral system

· Airway assessment by Mallampati grading

INVESTIGATIONS/INTERVENTIONS:

· Routine investigations, which include CBC, RBS, ECG, BT, CT, Chest X-ray, HIV, HbsAg, HCV, 2 D ECHO and Urine routine, were done.

PROCEDURE:

· Procedure was explained to the patient and patient attender.

· Written informed consent was taken prior to the procedure.

· Patients were kept on NPO for 6 hrs before surgery.

· After shifting the patient to the preoperative room, the patient's vital parameters were recorded.

· Patients were divided into two groups, Group A and Group B, by envelope picking method

·Patients were shifted to the operation theatre table.

· All ASA standard monitoring devices were attached.

1. Pulse rate(PR),
2. Non-invasive blood pressure(NIBP)
3. Oxygen saturation(SpO2)
4. Electrocardiogram (ECG)
5. Temperature probe
6. ETCO2

· After attaching the standard monitoring devices, the baseline vital parameter values were recorded just before the induction of the patient and it is noted as the Time – 0.

· Patients were given IV Glycopyrrolate 0.01 mg/kg, IV. Ondansetron 0.1 mg/kg, IV. Midazolam 0.08 mg/kg was given as the premedication for analgesia IV Fentanyl 2 mcg/kg.

· Patients were pre-oxygenated with 100% oxygen by facemask for 3 minutes, and induction was done with IV propofol 2.5 mg/kg dose.

· Ventilation was checked, and after confirming the ability of ventilation

· In this study for RSI, depolarising muscle relaxants like Succinyl choline are avoided so as to compare only the side effects and cost of cisatracurium and atracurium specifically.

·.The neuromuscular blocking agents were given based on the group the patient belonged to. Group A patients were given IV Atracurium 0.5mg/kg body weight, and group B patients were given IV Cisatracurium 0.15mg/kg were given, and patients were ventilated for 3 minutes, and endotracheal intubation was done, tube position was confirmed with five-point auscultation, and for definitive confirmation, the endotracheal tube is connected to capnography and capnographic waveforms were noted on the monitor. Anaesthesia was maintained with a mixture of 50% N2O and 50% O2, and an inhalational agent for maintenance of anaesthesia was done with isoflurane (0.2%-1.2% vol%) and assisted then connected to the mechanical ventilator and maintained on low flow anaesthesia throughout the surgery.

· When the surgery was about to end, the administration of all anaesthetic agents, especially the neuromuscular blocking agents, was stopped, and when the patient

started having the spontaneous respiratory effort reversed with IV Neostigmine 0.05mg/kg and IV Glycopyrrolate 0.008mg/kg. Extubation was done after full reversal and when the patient obeys oral comments.

· Both groups were assessed for the ADVERSE DRUG REACTION and COMPARISON OF COST ANALYSIS.

· For the assessment of **adverse reactions** of the NMBA, the vital parameters such as SBP, DBP, PR, SpO2, and temperature were assessed at every 15-minute interval at 15min, 30min, 60min, 90min and 120min.

·The clinical features and other signs and symptoms noted in both groups of patients are Bradycardia, Tachycardia, Hypertension, Hypotension, Flushing, Collapse, Hyperthermia, Wheezing, Bronchial secretion, Bronchospasm, Laryngospasm, Dyspnea, Apnea, Erythema, Itching Urticaria , Acute quadriplegic myopathy syndrome, Myositis ossificans, Seizure Prolong recovery time, Injection reaction.

· For the **Cost analysis,** the drug dosing is given according to the weight of the patient. For group A patients the dose of the atracurium is 0.5mg/kg, and for Group B patients, the dose of cisatracurium is 0.15mg/kg.

· In terms of cost analysis, for the atracurium group, the brand used is Inj Artacil 25 mg/ 2.5 ml. That is, each ml 0.5ml contains 5mg/cc, and it costs 162.96 INR, and for every 5mg, the cost is 32.55, and for each 1 ml, the cost is 6.51 INR

· Similarly, for the cost analysis of the cisatracurium group, the brand used is Inj Cis article 20mg/ 10 ml that. Each ml contains 2mg/cc, and its 10 ml cost is 891 INR rupees, and the cost of each ml that is every 1 mg cost is 44.55 INR

· For both groups, the total mg of drug used throughout the surgery is calculated, and the cost of the drug has also been calculated and entered in the proforma sheet.

SAMPLE SIZE CALCULATION

Sample size:

With anticipated proportion hypertension a adverse drug reaction atracurium and cistracurium drugs, 14 % and 0% (ref). Each study group would require a sample size of 70 for the investigation. (i.e., 140 total samples, assuming equal group sizes), in order to obtain an 80% power in identifying a two-sided p-value of 0.05 for a difference in proportions between two groups. Utilizing statulator software.

Formula used

$$n = \frac{(z\alpha + z\beta)\ 2\ 2\ p*q}{MD2}$$

Where Z= Z statistic at a level of significance

MD= Anticipated difference between two proportions

P=Common proportion

q= 100-p

sample size of 70 per group. (i.e. a total sample size of 140 assuming equal group sizes), to achieve a power of 85%

Statistical Analysis

The data obtained was entered in a microsoft excel sheet and statistical analysis was performed using statistical package for the social sciences (Verson 20).

The findings was displayed as Mean±SD, percentages, counts, and graphs.

To compare two sets of normally distributed continuous variables, the Independent t test was employed. The mann whitney U test was utilized for variables that are not regularly distributed. To compare categorical variables between two groups, the chi square test was employed. A p-value of less than 0.05 indicates statistical significance. Every statistical test was conducted two-tailed.

RESULT

TABLE NO.1 COMPARISON IN TERMS OF GENDER

GENDER	GROUPS		CHI SQUARE VALUE	P – VALUE
	ATRACURIUM	CISATRACURIUM		
MALE	33 (47.1%)	30 (42.9%)	0.260	0.610
FEMALE	37 (52.9%)	40 (55 %)		

In terms of gender, both atracurium and cisatracurium groups are statistically insignificant.

GRAPH NO 1. COMPARISON IN TERMS OF GENDER

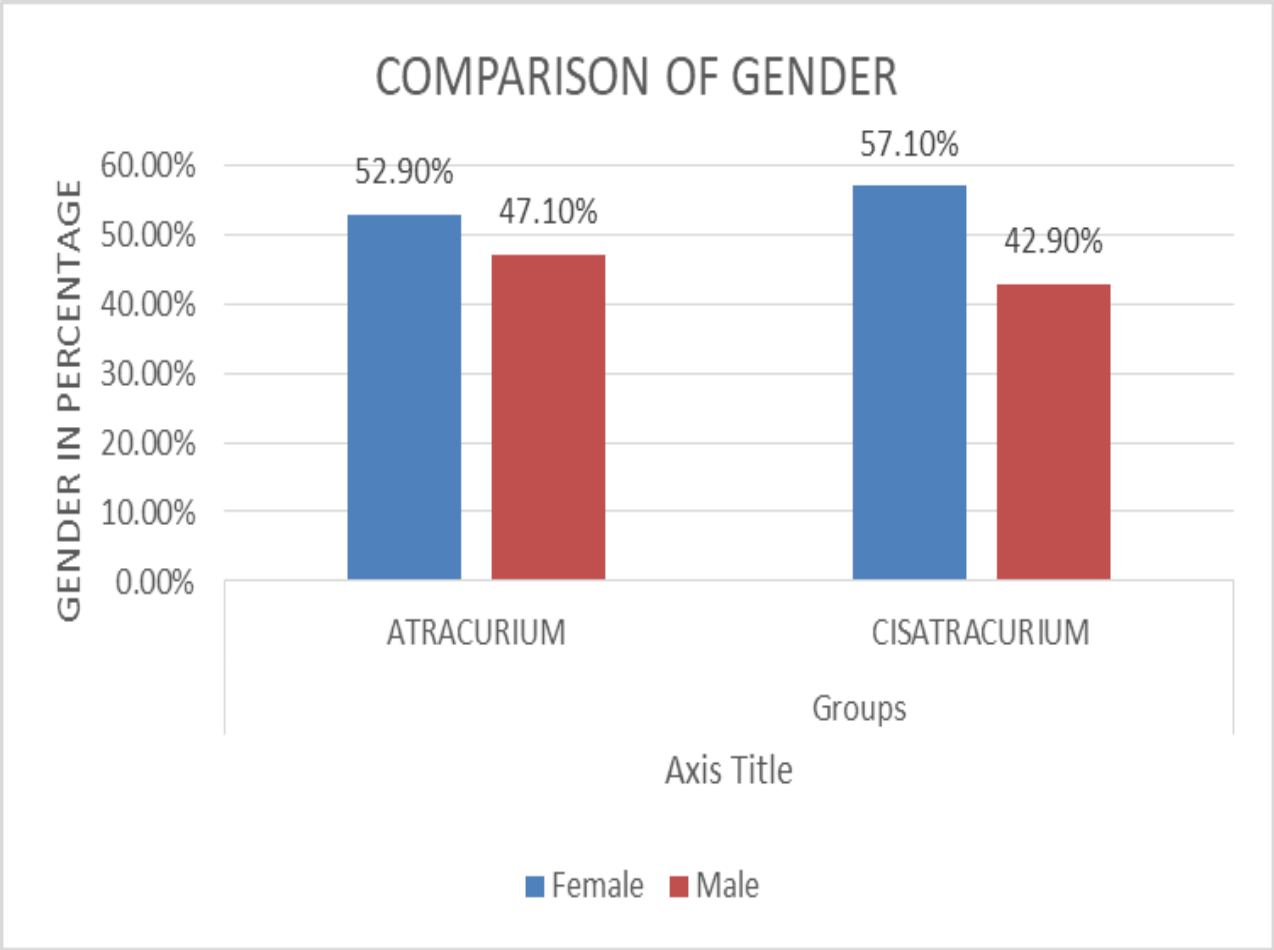


TABLE NO.2 COMPARISON IN TERMS OF BRADYCARDIA

BRADYCARDIA	GROUPS		CHI SQUARE VALUE	P - VALUE
	ATRACURIUM	CISATRACURIUM		
YES	1 (1.4 %)	1 (1.4 %)	0.00	1.0
NO	69 (98.6 %)	69 (98.6 %))		

In terms of bradycardia, both atracurium and cisatracurium groups are statistically insignificant.

GRAPH NO.2 COMPARISON IN TERMS OF BRADYCARDIA

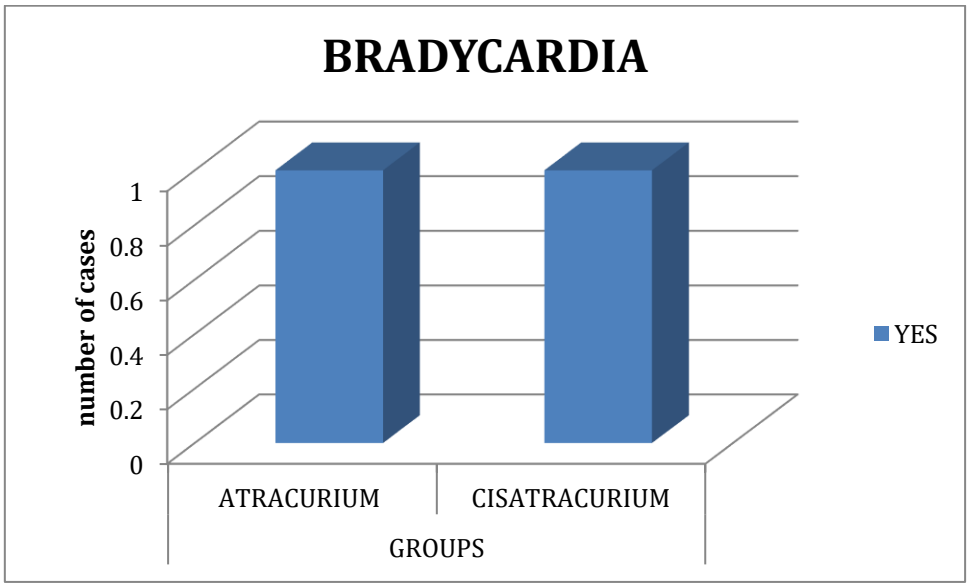


TABLE NO. 3 COMPARISON IN TERMS OF TACHYCARDIA

TACHYCARDIA	GROUPS		CHI SQUARE VALUE	P - VALUE
	ATRACURIUM	CISATRACURIUM		
YES	23 (32.9 %)	16 (22.9 %)	1.742	0.187
NO	47 (67.1 %)	54 (77.1 %))		

In terms of tachycardia, both atracurium and cisatracurium groups are statistically insignificant.

GRAPH NO. 3 COMPARISON IN TERMS OF TACHYCARDIA

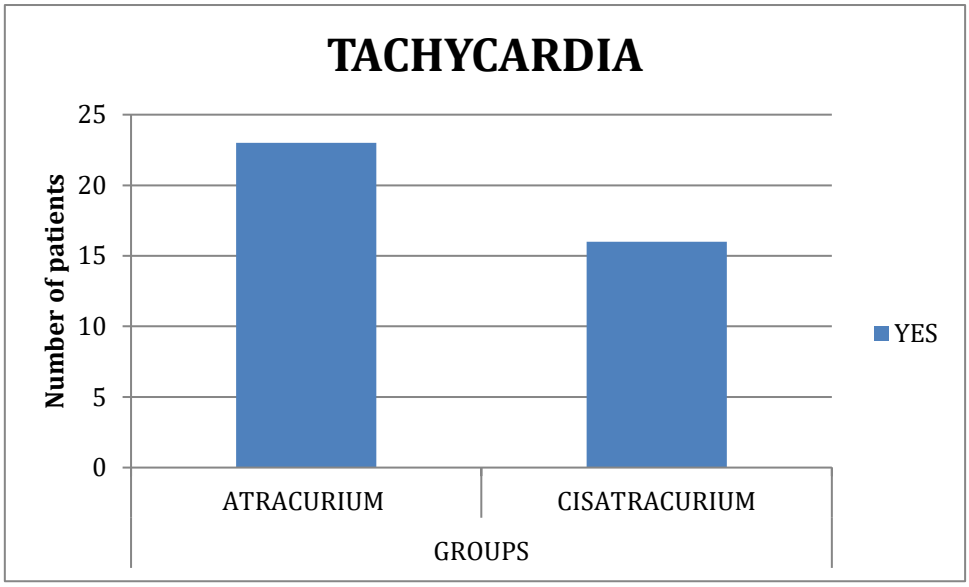


TABLE NO. 4 COMPARISON IN TERMS OF HYPERTENSION

HYPERTENSION	GROUPS		CHI SQUARE VALUE	P - VALUE
	ATRACURIUM	CISATRACURIUM		
YES	23 (32.9 %)	16 (22.9 %)	2.745	0.098
NO	47 (67.1 %)	54 (77.1 %))		

In terms of hypertension, both atracurium and cisatracurium groups are statistically insignificant.

GRAPH NO. 4 COMPARISON IN TERMS OF HYPERTENSION

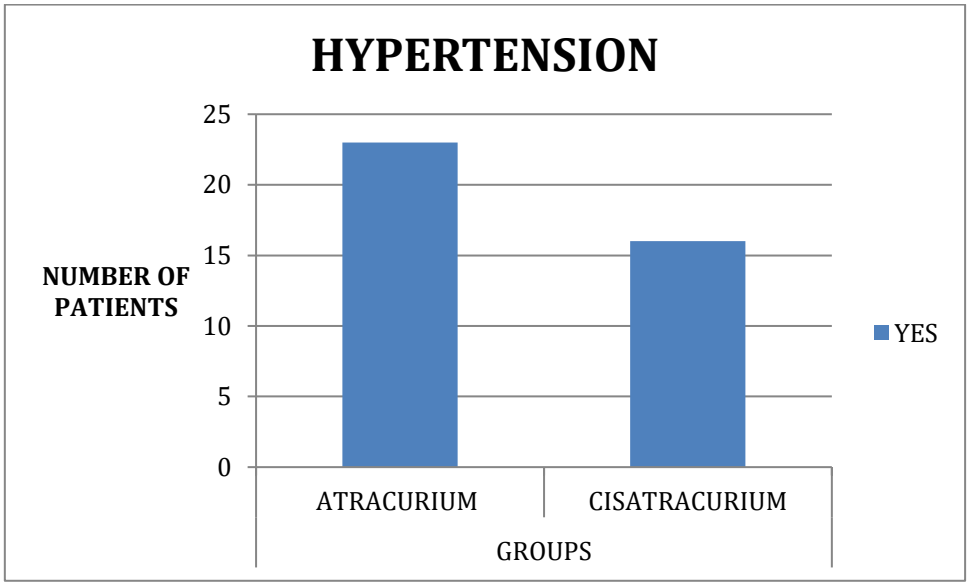


TABLE NO.5 .COMPARISON IN TERMS OF HYPOTENSION

HYPOTENSION	GROUPS		CHI SQUARE VALUE	P - VALUE
	ATRACURIUM	CISATRACURIUM		
YES	2 (2.9 %)	3 (4.3 %)	0.207	0.649
NO	68 (97.1 %)	67(95.7 %))		

In terms of hypotension, both atracurium and cisatracurium groups are statistically insignificant.

GRAPH NO.5 .COMPARISON IN TERMS OF HYPOTENSION

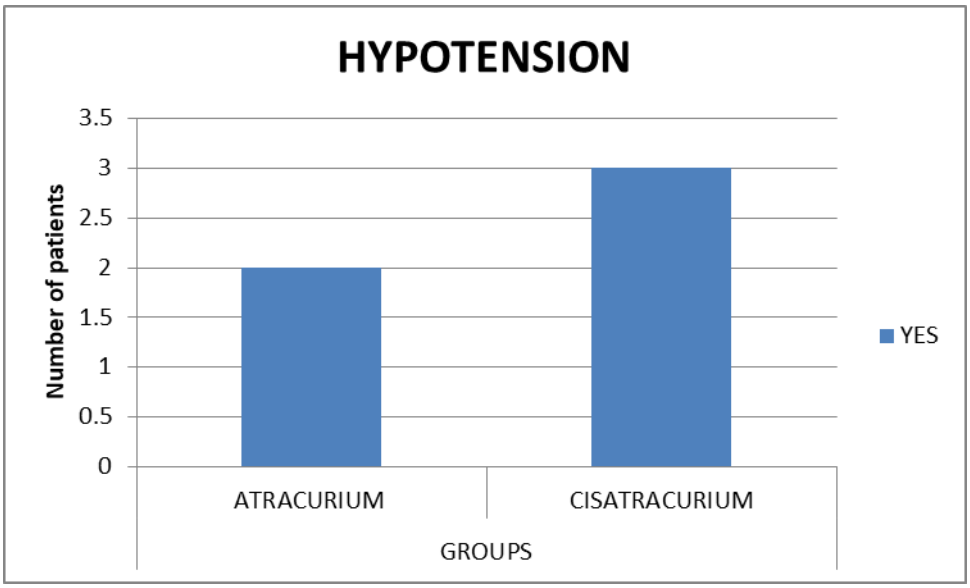


TABLE NO.6 .COMPARISON IN TERMS OF WHEEZING

	GROUPS		CHI SQUARE VALUE	P - VALUE
	ATRACURIUM	CISATRACURIUM		
YES	01(1.4 %)	00 (00%)	1.007	0.316
NO	69 (69.6 %)	70 (100%)		

In terms of wheezing, both atracurium and cisatracurium groups are statistically insignificant.

GRAPH NO.6 .COMPARISON IN TERMS OF WHEEZING

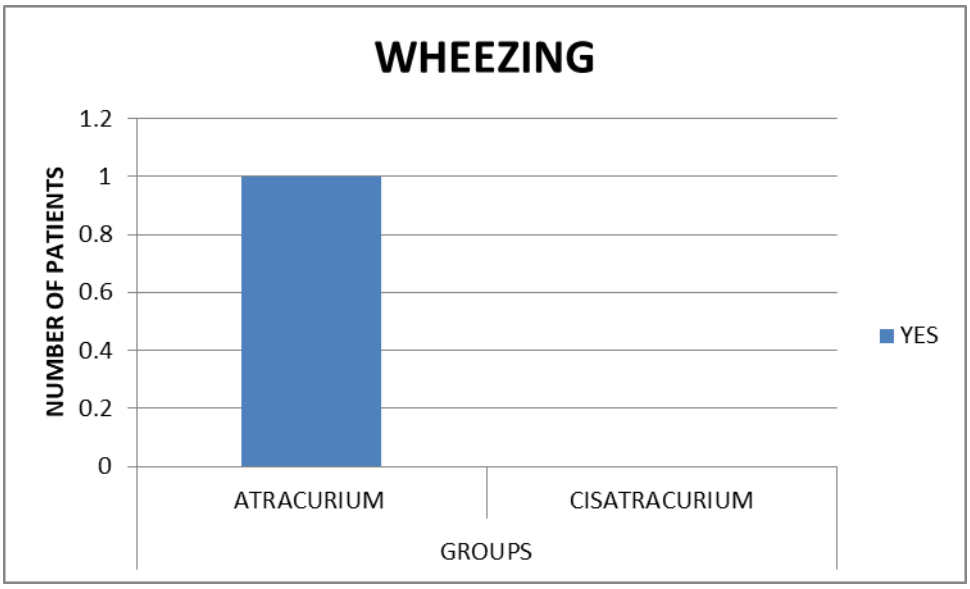


TABLE NO.7 COMPARISON IN TERMS OF AGE

Age	Groups			Chi square test	Significant value
	ATRACURIUM	CISATRACURIUM	Total		
< 20	7	5	12	5.904	P=0.316
	10.0%	7.1%	8.6%		
20 - 29	15	19	34		
	21.4%	27.1%	24.3%		
30 - 39	17	16	33		
	24.3%	22.9%	23.6%		
40 - 49	14	8	22		
	20.0%	11.4%	15.7%		
50 - 59	4	11	15		
	5.7%	15.7%	10.7%		
60+	13	11	24		
	18.6%	15.7%	17.1%		
Total	70	70	140		

In terms of gender both atracurium and cisatracurium groups are statistically insignificant

GRAPH No.7 COMPARISON IN TERMS OF AGE

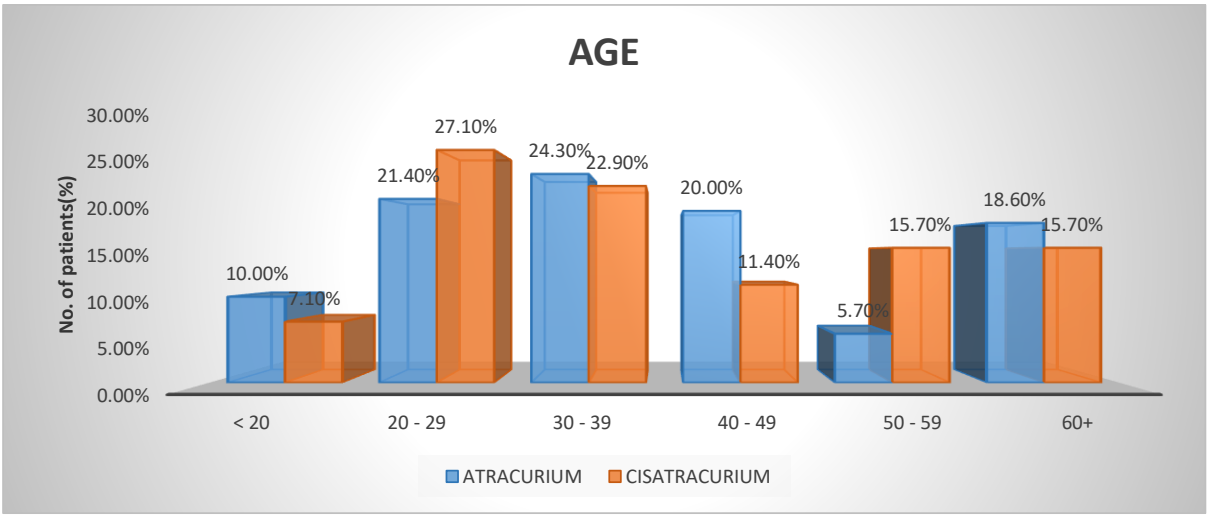


TABLE NO.8 COMPARISON IN TERMS OF COST

	GROUPS				MANN-WHITNEY U TEST	P - VALUE
	ATRACURIUM		CISATRACURIUM			
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION		
COST IN RUPEES	245.98	55.82	439.54	89.32	173.9	0.001

In terms of cost both atracurium and cisatracurium groups are statistically significant

GRAPH No.8 COMPARISON IN TERMS OF COST

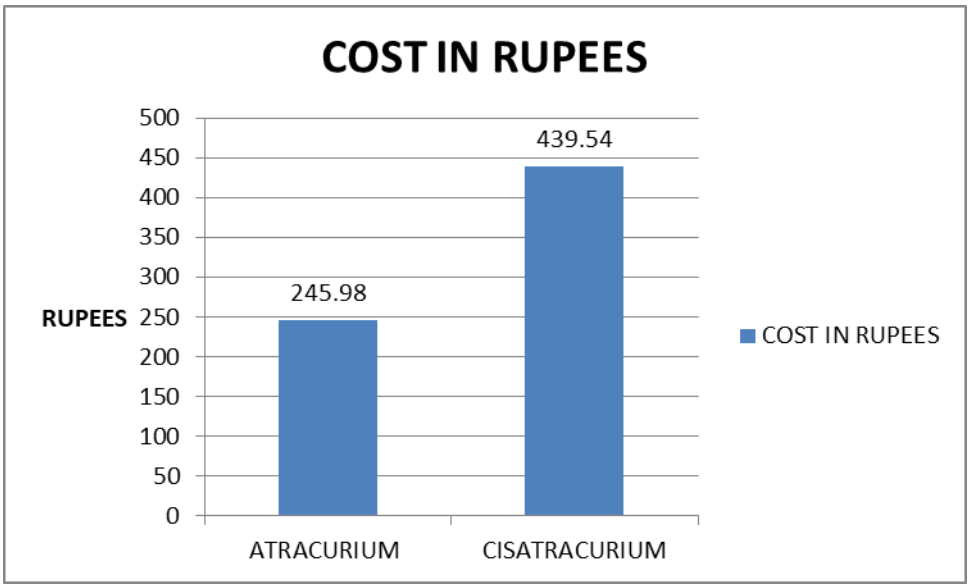
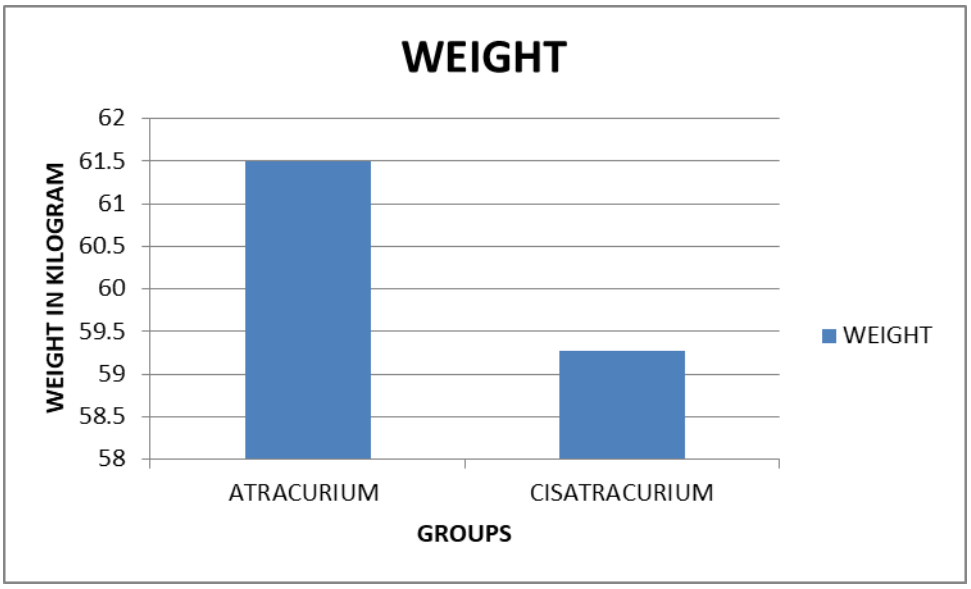


TABLE NO.9 COMPARISON IN TERMS OF WEIGHT

	GROUPS				KRUSHKAL WALLIS TEST	P - VALUE
	ATRACURIUM		CISATRACURIUM			
	MEAN	STANDARD DEVIATION	MEAN	STANDARD DEVIATION		
WEIGHT IN KG	61.5	10.8	59.27	9.75	1.778	0.18

GRAPH NO.9 COMPARISON IN TERMS OF WEIGHT



DISCUSSION

This study was done to compare the duration of action, first dose, and recovery of two non-depolarizing muscle relaxants with intermediate duration of action: atracurium and cisatracurium. Throughout the duration of the surgical procedure under general anaesthesia, hemodynamic parameters such as heart rate, systolic and diastolic blood pressure, mean arterial pressure and 60 minutes were recorded every 0 minutes, 15 minutes, 30 minutes, 60 minutes, 90 minutes, and 120 minutes.

Neuromuscular blockers (NMB) have been an essential component in the armament of anaesthetists. They lessen the need for anaesthesia, help with mechanical breathing and endotracheal intubation, make lengthy procedures more easy, and use less oxygen. The optimal neuromuscular blocking agent should not cause any adverse effects, act quickly to generate good intubating conditions, act for an intermediate to brief period of time, regulate the airway quickly, and allow for sufficient recovery and cardiovascular stability. When contrasting two neuromuscular blocking medications, it's crucial to consider certain factors such as adverse reaction, drug safety profile, and costs.

In the present study, for both drugs, adverse drug reactions and drug safety profiles were compared. Differences between adverse reactions of these drugs (atracurium and cisatracurium) were statistically insignificant. In Atracurium

group, the incidence of side effects like tachycardia, bradycardia and wheezing was more when compared to cisatracurium which was statistically insignificant.

MOVAFEGH et al. conducted a study in 2013, comparing the two study drugs, it was determined that there were statistically insignificant differences in the adverse reactions of these drugs (atracurium and cisatracurium) and that their safety profiles and adverse drug reactions were similar.

MANISHA BAGHAT et al conducted a study in 2018, to evaluate the adverse drug reactions (ADRs) within the atracurium group which was higher than that of the cisatracurium group, but this difference was not statistically significant. To assess the safety profile and differences between cisatracurium and atracurium, which are commonly used in adult patients for general anesthesia.

USHA BADOLE et al. conducted a study in 2021. It was concluded that patients who received six times the recommended dosage of cisatracurium (ED95) had better results than those who received two times the recommended dosage of atracurium (ED95). These patients had faster onset of action, better intubating conditions, better hemodynamic stability, longer duration of action, and no side effects.

Drug costs vary between countries as well as between hospitals within a same country. In addition, the cost of medications is a dynamic and active process; therefore, pharmacoeconomic analyses should be carried out to determine the most suitable medication regimen in light of changing drug prices and clinical practices. Drug costs in hospitals are influenced by various factors.

For instance, the cost of pharmaceutical units, insurance policies, and certain indirect elements like the price of treating adverse effects or reversing the effects of a treatment. Furthermore, the availability of pharmacological dosage forms significantly impacted the treatment's overall cost.

In our practice, cisatracurium and atracurium were available as 20 mg/10 ml and 25 mg/2.5 ml vials, respectively. The mean cost of atracurium was 245.98 INR, and cisatracurium was 439.54 INR. There was a significant difference in cost between the two NMBs (p-value of 0.001). Based on our study, we recommend the use of cisatracurium when a haemodynamic instability is suspected and atracurium in the remaining cases as it has a lesser cost. If just one neuromuscular blocking drug can be included in the drug formulary we would select cisatracurium due to its pharmacological advantages over atracurium with a small increment in cost.

MOVAFEGH **et al.** concluded in their study that atracurium and cisatracurium had comparable safety profiles and, at first loading dosages, atracurium was more cost-effective than cisatracurium. When patients' hemodynamic values were unstable, cisatracurium was the better choice.

CONCLUSION

The purpose of this study was to assess the adverse drug reaction, safety and effective cost analysis between the two intermediately acting NMBAs like atracurium and cisatracurium . The study involved 170 adults in the ASA I and ASA II classes, ranging in age from 18 to 80 years, who were undergoing various surgeries under general anaesthesia. Patients were randomly divided into two groups. Group A (Atracurium group, n=70), Group B (Cisatracurium, n=70). Group A (Atracurium group): Patients received 0.5 mg IV of atracurium. Group B (Cisatracurium): Patients received 0.15 mg of Cisatracurium IV hemodynamics like MAP, PR, Spo2, ECG and other clinical features and adverse reactions. Also, the cost of the drug was assessed. In terms of side effects, both drugs provide a similar safety profile, and cisatracurium is slightly a safer drug as it does not cause much hemodynamic changes and nil histamine release and can safely used in asthma and other histamine related disorders. In terms of cost comparison, Atracurium has economic benefits than cisatracurium.

SUMMARY

The purpose of this study was to assess adverse drug reactions, safety, and effective cost analyses of the two intermediately acting NMBAs, atracurium and cisatracurium. The study involved 170 adults in the ASA I and ASA II classes, ranging in age from 18 to 80 years, who were undergoing various surgeries under general anaesthesia. Patients were randomly divided into two groups. Group A (Atracurium group, n=70), Group B (Cisatracurium, n=70). Group A (Atracurium group): Patients received 0.5 mg IV of atracurium. Group B (Cisatracurium): Patients received 0.15 mg of Cisatracurium IV Respectively just before intubation, and 1/5th of the intubating dose was given for maintenance. The hemodynamics like MAP, PR, Spo2, ECG and other clinical features and adverse reactions and the cost of the drug were assessed. In terms of side effect, both drugs provide a similar safety profile, and cisatracurium is slightly a safer drug as it does not cause many hemodynamic changes and nil histamine release and can safely be used in asthma and other histamine related disorders. In terms of cost comparison, Atracurium has economic benefits than cisatracurium.

BIBILOGRAPHY

1. Matthew R, Belmont Cynthia A, Lien Steve Quessy, Martha M, Abou-Donia, Amy Abalos et al. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology. 1995; 82:1139-1145.

2. MOORE EW, HUNTER JM. The new neuromuscular blocking agents: do they offer any advantages. Br J Anaesth 2001; 87: 912-925.

3. MERTES PM, LAXENAIRE MC. Adverse reactions to neuromuscular blocking agents. Curr Allergy Asthma Rep 2004; 4: 7-16.

4. Lundstrøm LH, Duez CH, Nørskov AK, Rosenstock CV, Thomsen JL, Møller AM, Strande S, Wetterslev J. Effects of avoidance or use of neuromuscular blocking agents on outcomes in tracheal intubation: a Cochrane systematic review. British journal of anaesthesia. 2018 Jun 1;120(6):1381-93.

5. Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G, Lineberry C, Cato AE (1982). "Clinical pharmacology of atracurium

besylate (BW 33A): a new non-depolarizing muscle relaxant". Anesthesia and Analgesia. 61 (9): 723–729.

6. William B. Wastila, PhD; Robert B. Maehr, BS; Geoffrey L. Turner, PhD.; Derek A. Hill; M. Phil.; et al Comparative Pharmacology of Cisatracurium (51W89), Atracurium, and Five Isomers in Cats Anesthesiology 7 1996, Vol.85, 169-177

7. Bryson HM, Faulds D. Cisatracurium besilate. Drugs. 1997 May 1;53(5):848-66.

8. Jean-Yves Lepage, Jean-Marc Malinovsky, Myriam Malinge, Thierry Lechevalier, Christine Dupuch, Antonie Cozian et al. Pharmacodynamic doseresponse and safety of cisatracurium (51W89) in adult surgical patients during N2O-O2-Opioid anesthesia. Anesth Analg. 1996; 83:823-

9. Carroll MT, Mirakhur RK, Lowry DW, McCourt KC, Kerr C. A comparison of the neuromuscular blocking effects and reversibility 0f cisatracurium and atracurium, Anesthesia. 1998; 53:744.

10. 6.Smith CE1 van Miert MM, Parker CJ, Hunter JM. A comparison of the infusion pharmacokinetics and pharmacodynamics of cisatracurium, the 1R-

cis 1'R-cis isomer of atracurium, with atracurium besylate in healthy patients. Anaesthesia. 1997 Sep;52(9):833-41.

11. SPARR HJ, BEAUFORT TM, FUCHS-BUDER T. Newer neuromuscular blocking agents how do they compare with established agents.Drugs 2001; 61: 919-942

12. Smith G, D'Cruz JR, Rondeau B, et al. General Anesthesia for Surgeons. [Updated 2023 Aug 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK493199/

13. Oh SK, Kwon WK, Park S, Ji SG, Kim JH, Park YK, Lee SY, Lim BG. Comparison of Operating Conditions, Postoperative Pain and Recovery, and Overall Satisfaction of Surgeons with Deep vs. No Neuromuscular Blockade for Spinal Surgery under General Anesthesia: A Prospective Randomized Controlled Trial. J Clin Med. 2019 Apr 12;8(4) [PMC free article: PMC6518127] [PubMed: 31013693]

14. Robert k stoetling, Simon C Hillier.Pharamacology and physiology in anaesthetic practice.5th edition. philadelphia: lippimcott Williams an wilkins ;2006

15.Donate F. Neuromuscular blocking agent. In: Barash PG, Cullen BF, Stoetling RK, Cahalan MK, Clinical Anaesthesia.7thed. Philadelphia;Lipincott Williams and Wilkins; 2013.P.540

16. Barrow MEH, Johnson JK. A Study of anticholinesterase an anticurare effects of some cholinesterase inhibitors.Br J Anaesthesia;38:420-431

17.Feldman a, Fauvel N.Recovery from neuromuscular block. In : Polland B, ed. Applied neuromuscular pharmacology.Oxford :oxford university press,1994:107-22

18.Kirkegaard-Nielsen h, Helho-Hansen,Linholm P, Severinsen I K. Optimum time for neostigmine reversal of atracurium induced neuromuscular blockade-.Can J Anaesth 1996;43:932-8

19.Kitts JB, Fisher DM, Canfell PC, Spellman MJ, Caldwell JE, Heier T, et al.Pharmacokinetics and pharmacodynamics of atracurium in the elderly. Anesthesiology 1990;72:272-5

20. Basta SJ, Ali HH, Savarese JJ. Clinical pharmacology of atracurium besylate: a new non depolarizing muscle relaxant. AnaesthAnalg 1992;61:723-29.

21. Duggappa AK, Mathew S, Kordcal AR, Chakravarthi A, Muhamed S. Prospective comparative randomized controlled study to determine the optimal priming dose of atracurium. Indian J Respir Care 2018;7:42-5

22. Barrow MEH, Johnson JK. A Study of anticholinesterase an anticurare effects of some cholinesterase inhibitors.Br J Anaesthesia;38:420-431

23. Bryson HM, Faulds D. Cisatracurium besilate. A review of its pharmacology and clinical potential in anaesthetic practice. Drugs. 1997 May;53(5):848-66. doi: 10.2165/00003495-199753050-00012. PMID: 9129870.

24. Ghorbanlo M, Mohaghegh MR, Yazdanian F, Mesbah M, Totonchi Z. A Comparison Between the Hemodynamic Effects of Cisatracurium and Atracurium in Patient with Low Function of Left Ventricle who are

Candidate for Open Heart Surgery. Med Arch. 2016 Jul 27;70(4):265-268. doi: 10.5455/medarh.2016.70.265-268. PMID: 27703286; PMCID: PMC5034980.

25. Khobragade M, Sonwane RB. Comparative study of atracurium and cisatracurium for intubating conditions under general anaesthesia. IOSR J Dent Med Sci. 2020;19(2):52-6.

26. Subha PD, Jeyalakshmi BK, Ananda M. A prospective randomized comparative study of the efficacy of atracurium and cisatracurium during general anaesthesia. Int J Med Anaesth. 2020;3:122-6.

27. SAHU A, SWAIN S, SAMAL S, MOHANTY S. Efficacy of atracurium versus cisatracurium in patients undergoing retrograde cholangiopancreatography procedure under general anaesthesia–a comparative study. Group. 2020;10(20):30.

28. Kale J, Mahadik HA, Korde PM. A comparative study of Atracurium and Cisatracurium for assessment of intubating conditions. IJMA. 2020;3(3):24-7.

29. Rajan US. A comparative study of onset, duration and intubating conditions of cisatracurium and atracurium during general anesthesia.

30. Badole U, Gupta S, Sankar U, Patel KA. Comparison between cisatracurium and atracurium during general anaesthesia for abdominal surgery. IJMA. 2021;4(3):172-7.

31. Goyal P, Mathur A. Dr. Ashwin Sharma, Resident, Department of Anaesthesiology, GR Medical College Gwalior MP Dr. Shreyal Agarwal, Resident, Department of Anaesthesiology, GR Medical College Gwalior MP 2.

32. Patil S, Prasad AK, Negi R, Gogna RL. comparison between recovery profile of repeated bolus dose and continuous infusion of cisatracurium in patients undergoing prolonged surgeries using train of four: a prospective study. Int J Acad Med Pharm. 2022;4(4):228-31.

33. Hama AA, Hoobi NF, Majeed SE. Comparison between Rocuronium and Atracurium Effect on Blood Pressure during General Anaesthesia in Baghdad Hospital. Journal of Techniques. 2021 Mar 30;3(1):13-9.

ANNEXURE

I. INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

BLDE
(DEEMED TO BE UNIVERSITY)
Declared as Deemed to be University u/s 3 of UGC Act, 1956
Accredited with 'A' Grade by NAAC (Cycle-2)
The Constituent College
SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

BLDE (DU)/IEC/ 777/2022-23 30/8/2022

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this University met on **Friday, 26th August, 2022 at 3.30 p.m. in the Department of Pharmacology** scrutinizes the Synopsis of Post Graduate Student of BLDE (DU)'s Shri B.M.Patil Medical College Hospital & Research Centre from ethical clearance point of view. After scrutiny, the following original/ corrected and revised version synopsis of the thesis/ research projects has been accorded ethical clearance.

TITLE: "Cost analysis and safety Comparison of cisatracurium and Atracurium in patient undergoing General anaesthesia".

NAME OF THE STUDENT/PRINCIPAL INVESTIGATOR: Dr.Arun Kumar T V

NAME OF THE GUIDE: Dr.Vijaykumar T K, **Dept. of Anaesthesiology**

Dr. Santoshkumar Jeevangi
Chairperson
IEC, BLDE (DU),
VIJAYAPURA.

Chairman,
Institutional Ethical Committee,
BLDE (Deemed to be University)
Vijayapura

Dr.Akram A. Naikwadi
Member Secretary
IEC, BLDE (DU)
VIJAYAPURA

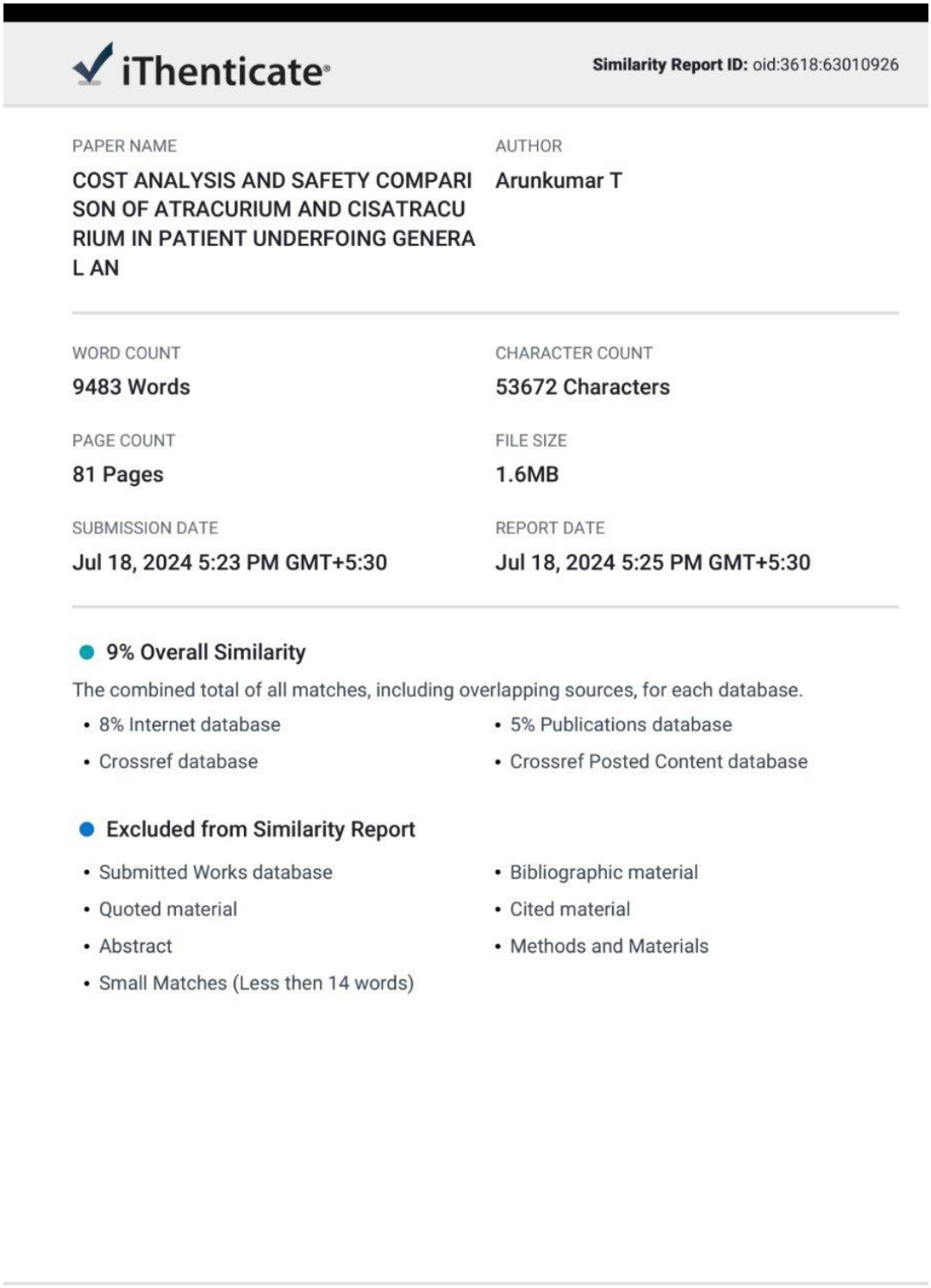
MEMBER SECRETARY
Institutional Ethics Committee
BLDE (Deemed to be University)
Vijayapura-586103. Karnataka

Following documents were placed before Ethical Committee for Scrutinization.

- Copy of Synopsis/Research Projects
- Copy of inform consent form
- Any other relevant document

Smt. Bangaramma Sajjan Campus, B. M. Patil Road (Sholapur Road), Vijayapura - 586103, Karnataka, India.
BLDE (DU): Phone: +918352-262770, Fax: +918352-263303, Website: www.bldedu.ac.in, E-mail:office@bldedu.ac.in
College: Phone: +918352-262770, Fax: +918352-263019, E-mail: bmpmc.principal@bldedu.ac.in

II. PLAGIARISM CERTIFICATE SCREEN SHOT



iThenticate

Similarity Report ID: oid:3618:63010926

PAPER NAME
COST ANALYSIS AND SAFETY COMPARI SON OF ATRACURIUM AND CISATRACU RIUM IN PATIENT UNDERFOING GENERA L AN

AUTHOR
Arunkumar T

WORD COUNT
9483 Words

CHARACTER COUNT
53672 Characters

PAGE COUNT
81 Pages

FILE SIZE
1.6MB

SUBMISSION DATE
Jul 18, 2024 5:23 PM GMT+5:30

REPORT DATE
Jul 18, 2024 5:25 PM GMT+5:30

9% Overall Similarity

The combined total of all matches, including overlapping sources, for each database.

- 8% Internet database
- 5% Publications database
- Crossref database
- Crossref Posted Content database

Excluded from Similarity Report

- Submitted Works database
- Bibliographic material
- Quoted material
- Cited material
- Abstract
- Methods and Materials
- Small Matches (Less then 14 words)

III. PATIENT INFORMED CONSENT FORM

B.L.D.E (Deemed to be University)

SHRI B.M PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYPURA-586103, KARNATAKA

TITLE OF THE PROJECT:

COST ANALYSIS AND SAFETY COMPARISON OF ATRACURIUM AND CISATRACURIUM IN PATIENT UNDERGOING GENERAL ANAESTHESIA

PRINCIPAL INVESTIGATOR: DR. TV.ARUN KUMAR

Department of Anaesthesiology

BLDE (Deemed to be University)

Shri B.M Patil Medical College and Research Centre, Sholapur Road

Vijaypura-586103

PG GUIDE: DR. VIJAYKUMAR T.K

Department of Anesthesiology BLDE (Deemed to be University) Shri B.M Patil Medical College Research Centre, Sholapur Road Vijaypura-586103 I have been informed that this study is “cost analysis and safety comparison of atracurium and cisatracurium in patient undergoing general anaesthesia". I have been explained about this study in the language which I understand. I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have been told that my participation in the above study is voluntary, and I am aware that I can opt-out of the study at any time without having to give any reasons for doing so. I am also informed that my refusal to participate in this study will not affect my treatment by any means. I agree to participate in the above study and cooperate fully. I agree to follow the doctor’s instructions about my treatment to the best of my knowledge.

CONFIDENTIALITY: I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records but will be stored in the investigator's research file and identified only by a code number. The code key connecting the name to numbers will be kept in a separate secure location. If the data are used for publication in the medical literature or teaching purposes, no names will be used, and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I

understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION: I understand that I may ask more questions about the study at any time, and Dr T.V. ARUN KUMAR available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation. If during this study, or later, I wish to discuss my participation or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me and that a copy of this consent form will be given to me for my careful reading

REFUSAL OR WITHDRAWAL OF PARTICIPATION: I understand that my participation is voluntary, and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr T.V .ARUN KUMAR will terminate my participation in this study at any time after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly to my participation in this study, if such injury were reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights. I have been explained the purpose of this research, the procedures required, and the possible risks and benefits, in my own language. I have been explained all the above in detail, and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

Patient's Signature: Witness Signature:

Name:

Date:

DR. VIJAYKUMAR.T.K DR.T.V.ARUN KUMAR

(Guide) (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that DR. T.V. ARUN KUMAR has explained to me the purpose of this research, the study procedure that I will undergo, and the possible discomforts and benefits that I may experience in my own language.

I have been explained all the above in detail in my own language, and I understand the same. Therefore, I agree to give my consent to participate as a subject in this research project.

Participant: Date:

Witness to the above signature Date

IV. PROFORMA

COST ANALYSIS AND SAFETY COMPARISON OF CISATRACURIUM AND ATRACURIUM IN PATIENT UNDERGOING GENERAL ANAESTHESIA

DATE

CASE NO.

Patient Details

Name

Age

Sex

Weight

Group allotted by randomization: A/B

Diagnosis

Surgical procedure

Past History

General physical examination:

Pallor icterus cyanosis clubbing lymphadenopathy edema

Mallampatti Grade:

Intra operative Vital parameters:

	BP	PR	SpO2	RR
0 min				
30 min				
60 min				
90 min				
120 min				

ADVERSE REACTIONS	**ATRACURIUM**	**CISATRACURIUM**	
CARDIOVASCULAR Bradycardia Tachycardia Hypertension Hypotension Flushing Collapse			

RESPIRATORY Hyperthermia Wheezing Bronchial secretion Bronchospasm Laryngospasm Dypsnea Apnea			
SKIN Erythema Itching Urticaria			
MUSCULOSKELETAL Acute quadriplegic myopathy Myositis ossificans			

OTHERS Seizure Prolonged recovery time Injection rteaction			

COMPARISON OF TWO GROUP IN COST

Drug		
ATRACURIUM		
CISATRACURIUM		

MRP of the drug :

CVS

RS

CNS

PA

Investigations

Hemoglobin: TLC:

Platelet count:

Urine routine: HIV: HbsAg:

ASA grade

POST OPERATIVE VITAL PARAMETERS

Time	Pulse Rate	Blood Pressure	Mean Arterial Pressure	SpO2	Respiratory Rate
0 mins					
15 mins					
30 mins					
45 mins					
60 mins					

V. GUIDE BIO DATA

Professor Guide Name : Dr. Vijaykumar T Kalyanappagol

Date of Birth : 08/09/1964

Education : MBBS from M R Medical College Kalaburgi

M D from Shri BM PATIL Medical college

Vijayapur,

D A from JN Medical College Belgaum

KMC RegNo. :28014

Designation : Professor in Anesthesiology

Teaching :Total work experience 32 years

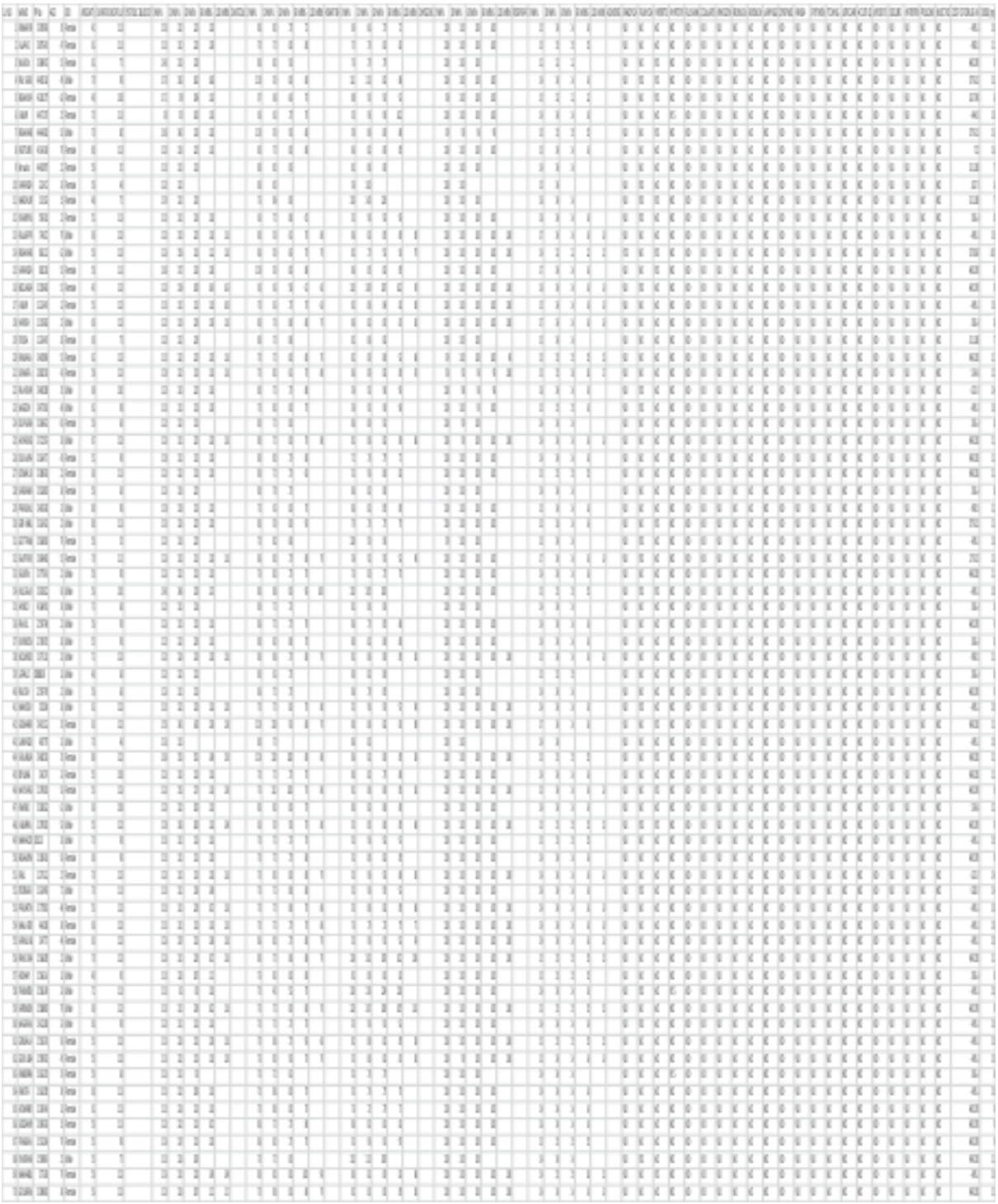
PG teaching 24 years

PG guide 15 years

Address :Plot No.43, Basaveshwar Nagar, Opposite BLDE Hospital, Ashram Road,Vijayapura.

VI.MASTER CHART

CISATRACURIUM GROUP



ATRACURIUM GROUP