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Comparison Between Glycopyrrolate And Atropine as a Premedicant on Hemodynamic Stability in Pediatric Anesthesia

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Abstract

Background: Most (82%) arrests in pediatric anesthesia was occurred during induction of anaesthesia;bradycardia, hypotension, and a low spo2 were frequent preceding events. The most common mechanism of cardiac arrest was judged to be medication related. Cardiovascular depression from halothane alone or in combination with other drugs, was believed to be responsible in 66% of all medication related arrests.
Aim of study: To compare between glycopyrrolate and atropine as a premedicant on haemodynamic stability in paediatric anaesthesia.
Patient and method: An interventional clinical trial was carried out in Pedeatric Surgery theatres of Baghdad Teaching Hospital.40 pediatric patients divided in two groups A and B. Group A:20 patients, Who received glycopyrrolate 0.004mg/kg as premedication.Group B: 20 patients, who received atropine 0.02mg/kg as premedication. Anesthesia was induced with an analgesic dose of ketamine 0.5mg/kg, induction dose of thiopental up to 3-5 mg/kg and tracheal intubation (with size according to the age of the patient) was facilitated with 0.5 mg/Kg of atracurium. Anesthesia was maintained with halothane 0.6-1.0% in 100% oxygen and i.v fluid. Neuromuscular blockade was maintained with incremental doses of 0.1mg/kg atracurium. Reversal dose giving at the end of the operation. Monitoring O2 saturation, NIBP, ECG and pulse rate. Result: By using the SPSS V.20/IBM using the t-student test and the chi square it was found there is no significant differences between the Atropine group and glycopyrolate group in age, weight, blood pressure. Basal pulse rate and pulse rate at 10 minutes and above were the p-values were above 0.05.There are significant differences between glycopyrolate group and atropine groups at 1 minutes after test dose, after intubation, 5minutes after and 10 minutes after. Conclusion: Patients who received Glycopyrrolate were more haemodynamic stable than those who received atropine regarding change in pulse rate in the first 15 minutes

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1 INTRODUCTION

Anticholinergic drugs competitively antagonize the effects of the neurotransmitter acetylcholine at cholinergic postganglionic sites designated as muscarinic receptors.

Muscarinic cholinergic receptors are presented in the heart, salivary gland and smooth muscles of the gastrointestinal and genitourinary tract. (1)

MECHANISM OF ACTION:-

Anticholinergic drugs combine reversibly with muscarinic cholinergic receptors and thus prevent access of the neurotransmitter acetylcholine to these sites. As competitive antagonists. The effect of anticholinergic drugs can be overcome by increasing the concentration of acetylcholine in the area of the muscarinic receptors.Five distinct muscarinic receptors subtypes, with recognized tissue distributions, are designated M1-M5. Muscarinic receptors are examples of G protein-coupled receptors that also depend on second-messenger coupling. (1)

Glycopyrrolate: -

Action and Clinical Pharmacology: Glycopyrrolate, like other anticholinergic (antimuscarinic) agents, competitively antagonizes the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. Glycopyrrolate antagonizes muscarinic symptoms (e.g., bronchorrhea, bronchospasm, bradycardia and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases.

As a premedicant, glycopyrrolate injectable reduces excessive pharyngeal, tracheal and bronchial secretions and, during anesthesia, it appears to protect the heart against excessive vagal stimulation. Glycopyrrolate's polar ammonium moiety limits its passage across lipid membranes, such as the blood-brain barrier in contrast to the belladonna alkaloids, which are nonpolar tertiary amines. Consequently, glycopyrrolate injectable does not cause CNS effects seen with the belladonna alkaloids.

The onset of action following i.m. glycopyrrolate injection is 20 to 40 minutes. Peak effects occur approximately 30 to 45 minutes after administration and the duration of action ranges from 4 to 6 hours. With i.v. injection, the onset of action is generally evident within

1 minute; the duration of action varies, as does that of all other anticholinergics. Following i.v. glycopyrrolate, the vagal blocking effects persist for 2 to 3 hours and the antisialagogue effects persist up to 7hours. (2)

Indications And Clinical Uses: The management of gastrointestinal disorders amenable to anticholinergic therapy when oral medication is not tolerated or a rapid anticholinergic effect is desired. May also be used as a preanesthetic antimuscarinic agent. During reversal of neuromuscular blockade induced by nondepolarizing muscle relaxants, it protects against the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) of cholinergic agents such as neostigmine and pyridostigmine. (2)

Contra-Indications: Known hypersensitivity to glycopyrrolate and in treatment of gastrointestinal disorders in the presence of glaucoma, obstructive uropathy (e.g., bladder neck obstruction due to prostatic hypertrophy), obstructive disease of the gastrointestinal tract (e.g., pyloroduodenal stenosis), paralytic ileus, intestinal atony or chronic lung disease of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis. Due to its benzyl alcohol content, Robinul Injectable should not be used in newborns. (3)

Precautions: The i.v. administration of any anticholinergic in the presence of cyclopropane anesthesia can result in ventricular arrhythmias; therefore, observe caution if glycopyrrolate injectable must be used during cyclopropane anesthesia. If the drug is given in small incremental doses of 100 μg or less, the likelihood of producing ventricular arrhythmias is reduced.

Investigate any tachycardia before giving anticholinergic (atropine like) drugs since they may increase the heart rate.

With overdosage, a curare like action may occur, i.e., neuromuscular blockade leading to muscular weakness and possible paralysis. However, it has not yet been reported.

Use glycopyrrolate injectable with caution in elderly and in all patients with autonomic neuropathy; hepatic or renal disease; ulcerative colitis (large doses may suppress intestinal motility to the point of producing a paralytic ileus and for this reason precipitate or aggravate the serious complication of toxic megacolon); hyperthyroidism;

coronary heart disease; congestive heart failure; cardiac arrhythmias; hypertension; prostatic hypertrophy; hiatal hernia associated with reflux esophagitis, since anticholinergic drugs may aggravate this condition; incipient glaucoma (acute glaucoma can be precipitated in susceptibl eindividuals). Anticholinergic drugs used in the treatment of gastric ulcer may produce a delay in gastric emptying time and may complicate such therapy (antral stasis). Consider the use of an indwelling nasogastric tube whenever more than 2 doses in succession are to be administered. Do not rely on the use of glycopyrrolate in the presence of complications of biliary tract disease. (3)

Adverse Reactions: Symptoms of CNS effects have not been observed with glycopyrrolate injectable. Adverse reactions to anticholinergics may include xerostomia; urinary hesitancy and retention; blurred vision due to mydriasis and cycloplegia; photophobia; increased ocular tension including acute glaucoma; tachycardia; palpitation; decreased sweating and heat prostration; loss of taste; headache; nervousness; drowsiness; weakness; dizziness, insomnia, nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis, urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons. (3)

Atropine:

It is the alkaloid of atropa belladonna and it is ester of tropic acid with organic base - tropine .atropine is the racemic mixture of dextrorotatory isomer and levorotatory isomer but levo isomer is more active. Atropine was first suggested by E.A.Sharpeyschaffer (1850-1935), an Edinburgh physioslogist, in 1880 to prevent vagal cardiac arrest during chloroform anesthesia, and advocated by Dudley Buxton (1855-1935),a London anesthetist, 35 years later to inhibit secretions during ether anesthesia (4)

Pharmacokinetics:

Atropine is a naturally occurring tertiary amine anticholinergic readily absorbed from site of injection and from alimentary tract, rapid onset of action this in part destroyed in the liver and in part excreted by the kidney. The does in neonate 0.04 mg / kg infant < 4 kg and 0.02 mg / kg infant > 4 kg (5).

Mechanism of action:

Atropine combine reversibly with muscarinic cholinergic receptors (subclasses Ml, M2 and M3) and thus prevent access of the neurotransmitter acetylcholine to these sites in contrast to the acetylcholine the combination of an anticholinergic drug with the muscarinic receptor does not result in cell membrane changes (4).

Action of atropine

1. Central Nervous System (CNS): mild stimulation to medulla and higher centers lead to restlessness and delirium are seen in poising dose.
2. Cardio-Vascular System (CVS): tachycardia occurs due to the inhibition of vagal influence on the sinoatrial node. Reflex bradycardia and Neostigmine-induced bradycardia are prevented, atropine is most reliable in preventing or treating bradycardia if given intravenously just before anesthesia and surgery'. Atropine can be considered for asystole, although it is no longer recommended as first-line treatment the tachycardia decreases coronary filling time and increases myocardial oxygen consumption and so it should be used with care in patients with coronary disease.Cardiac output and arterial pressure is usuallyincreased,withafallinCVP(3).
3. Respiratory System (RS): Sweat, bronchial and salivary glands are inhibited. Drying of airway secretion increased viscosity of airway secretion may be in patients with chronic pulmonary disease. The clinical significance of this effect in response to a single dose of anticholinergic as administered for pre-operative medication is unproven (5-8). Bronchial muscle is relaxed, causing bronchodilation. (4)
4. The eye: Topical atropine resulting dilated pupils and loss ofaccommodation for up to a week. Parenteral atropine has little effect on the eye and is not contra indicated in a patient with glucoma.
5. Gastro-Intestinal Tract (GIT) and Urinary System (US): The tone and peristalsis of the gut and urinary tract are decreased.
6. Effect on fetus: Atropine crosses the placenta rapidly and may protect the fetus and new born from vagal reflexes occurring during birth and resuscitation (4).

7. Body temperature : Anticholinergics may result in increased body temperature by suppressing sweat glands that are innervated by cholinergic nerves via the sympathetic nervous system (8-10).

***Anatomy and physiology of the autonomic nervous system*:**

The central autonomic nervous system includes the hypothalamus (stress responses, blood pressure control, temperature regulation) and vital centers for hemodynamic and ventilatory control in the medulla and pons. The peripheral autonomic nervous system is divided into the sympathetic and parasympathetic nervous system, figure l.1.(5)

The SA node and AV node receive autonomic nervous system via sympathetic and parasympathetic nervous systems eliciting change in heart rate in response to physiological changes within the body that vary with the individual age and particular situation (9)

- The parasympathetic nervous stimulation through the vagus nerve in related to this study cause On the A.V. node decrease in conduction velocity.

1- A decrease in heart rate via M2 muscarinic receptors, which lead to the following effect on the heart:
   - On the S.A. node decrease in automaticity.
   - On the atria decrease in contractility.
   - Maximal parasympathetic stimulation decrease cardiac Output about 30 % (4).
2- Cardiac stand-still.
3- Excessive bronchial secretion.
4- bronchospasm.(10)

The sympathetic stimulation through the cardiac accelerator nervous via the stellate ganglion increase the heart rate and force of contraction by stimulating the beta-receptors in the heart. The sympathetic nerve fibers to the heart continually discharge at slow rate that maintains strength of ventricular contraction about 20 - 25 % above its strength in the absence of parasympathetic stimulation. Maximal sympathetic stimulation can increase cardiac output by about 100 % above normal. (4)

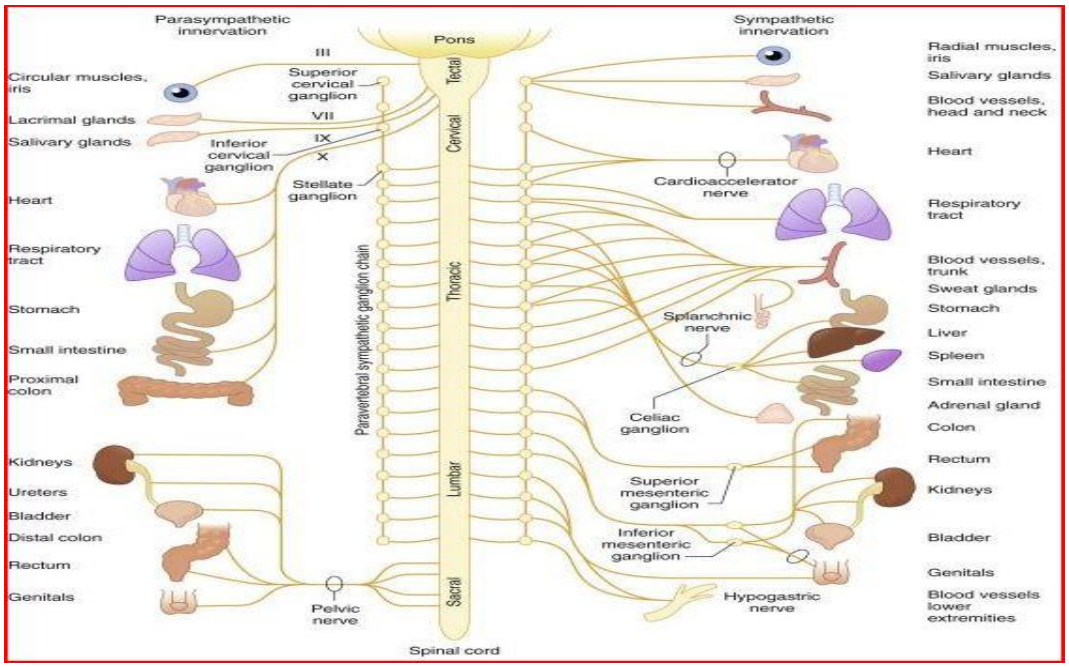

Figure 1. autonomic nervous system

Physiological deference between neonate and adult

1. In neonate the parasympathetic control of cardio-vascular system is well developed at birth but sympathetic control of cardio-vascular system is immature due to not fully innervation of heart with the sympathetic fiber and nor-adrenaline content of cardiac sympathetic nerves is less than in the adult (11). The decrease sympathetic neural output may explain: A- The normally low blood pressure in human infant. B- Increase susceptibility to reflex bradycardia and hypotension (10).
2. At birth resting cardiac output is 200 ml/kg/min. decline gradually to l00ml/kg/min. by adolescence. (11) Cardiac output is rate dependent. Bradycardia is common and often results in hypotension.
3. In neonate the normal resting heart rate varies between 120-160 beats/minute (7). This occurs because the relatively incompliant ventricular wall tend to limit the range of stroke volume (12) As a resting stroke volume remains fairly constant in neonate and adult about 1ml/kg. The neonate adjusted cardiac output to meet rapidly change metabolic demands primarily by altering heart rate rather than stroke volume.

4. A low level of baroreceptor activity in infant may reduce their ability to adapt to hypotension by an increase in heart rate (12) A heart rate that decline 20-30% below the normal level for neonate (eg-less than 100 beats/min) associated with the reduction in cardiac output (12).
5. Tiny respiratory airway .airway resistance (15-30) cm H2O/L/sec in compared to adult (1.5 -2) cm H2O/L/sec (12) and small endotracheal tube, which range between (2.5 - 3.5) mm internal diameter (7).

Reflex bradycardia:

Sudden reduction of heart rate more than 20% decrease in heart rate of neonate i.e less than 100 beat/min. reflex arrhythmia tend to occur during light anesthesia as a result of parasympathetic stimulation (13).

Causes of bradycardia:-

Potent causes of reflex bradycardia, hypotension and cardiac stand

still in infant during anaesthesia include:

1. Laryngoscopy
2. Tracheal intubation
3. Tracheal suction.
4. Traction on eye muscles and viscera.
5. Bradycardia may also cause by variety of an aesthetic Drugs including:
   - Suxamethonium
   - Halothane
   - Neostigmine (12)

2 PATIENTS AND METHODS

An interventional clinical trial was carried out in Pedeatric Surgery theatres of Baghdad Teaching Hospital, during the period from the first of Jan 2014 to the30thMarch 2014.Forty patients were included, who were operated on for GIT surgery.

Inclusion criteria:

The patients were included in the study if they met the following.

1. Gender both genders

2. Age: 1month – 6 years.
3. Patients of ASA grade I and II
4. Weight: 4-15 Kg
5. All patients were scheduled for elective GIT surgery.

Exclusion criteria:

1. Any Patient with CVS disease.
2. Any Patient on medical treatment affecting CVS system.
3. Any Patient with allergy to the drug used in the study.
4. Pre-term baby.
5. Parents refusal.

The consent and a detailed history was taken from the relative of each patient; information about the age of the patient and past medical history and the study was approved by the local committee of the scientific council of anesthesia and intensive care. A clinical examination was performed by general examination and vital signs measurement. The study was performed by measuring the PR by pulse oximeter and ECG electrode. Arterial pressures were measured non- invasively by cuff manometry before of the study drug, 1min. after test dose, immediately after tracheal intubation and extubating and at 5-min intervals thereafter until the end of the study.

Anesthetic management was standardized as follows:

All patients received 0.02mg/kg midazolam as pre-medication agent before anticholinergic drugs. Then all patients were divided randomly into two groups:

Group A: 20 patients, who received glycopyrrolate 0.004mg/kg as premedication.

Group B: 20 patients, who received atropine 0.02mg/kg as premedication.

Anesthesia was induced with an analgesic dose of ketamine 0.5mg/kg, induction dose of thiopental up to 3-5 mg/kg and tracheal intubation (with size according to the age of the patient) was facilitated with 0.5 mg/Kg of atracurium. Anesthesia was maintained with halothane 0.6-1.0% in 100% oxygen and i.v fluid. Neuromuscular blockade was maintained with incremental doses of 0.1mg/kg atracurium. Reversal dose giving at the end of the operation. Monitoring O2 saturation, NIBP ECG.

Statistical Analysis

Analysis of data was carried out using the available statistical package of SPSS-22 (Statistical Packages for Social Sciences- version 22). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of difference of different percentages (qualitative data) were tested using chi-square test (χ^2-test) with application of student-t test and the chi square Statistical significance was considered whenever the P value was equal or less

3 | RESULTS

No significant differences between the Atropine group and glycopyrrolate group in age, weight, blood pressure. Basal pulse rate and pulse rate at 10 minutes and above were the p-values were above 0.05. There are significant differences between glycopyrrolate group and atropine groups at 1 minutes after test dose, after intubation, 5 minutes after and 10 minutes after. None of the patient in both groups developed any arrhythmias, as shown in the tables and figures below

Table 1. Comparison of mean age of the studied groups

Statistics	Glycopyrrolate group	Atropine group
Mean (months)	7.367	7.557
SD (months)	3.719	2.445
P. value	0.771 NS	

SD: standard deviation of mean
NS: not significant > 0.05

Table 2. Comparison of mean weight of the studied groups

Statistics	Glycopyrrolate group	Atropine group
Weight (kg)	7.831	7.177
SD (kg)	1.233	1.557
P. value	0.641 NS	

SD: standard deviation of mean
NS: not significant > 0.05

Table 3. Comparison of mean pulse Rate between both groups

	Glycopyrolate		Atropine		P. value
	Mean	SD	Mean	SD	
Baseline (before midazolam)	118.8	22.6	116.1	25.3	0.574
1 min after test dose	120.7	21.9	155.6	22.8	0.014
After intubation	134.8	14.0	163.5	15.9	0.009
5 min	124.8	15.6	158.9	16.4	0.012
10 min	117.5	18.4	149.3	19.7	0.029
15 min	112.4	19.5	120.4	15.4	0.074
20 min	100.6	18.5	106.3	12.5	0.091
25 min	101.3	20.8	103.1	14.6	0.116
30 min	104.3	22.7	102.6	10.6	0.451
35 min	102.4	16.4	105.5	12.0	0.471
40 min	100.1	13.6	102.5	18.2	0.754
45 min	104.6	14.6	100.4	12.7	0.533
50 min	100.2	15.3	100.1	16.5	0.239
55 min	105.3	12.8	104.5	12.5	0.891
60 min	100.6	11.6	101.0	15.8	0.678

Table 4. Comparison of Systolic blood pressure between both groups

	Glycopyrolate		Atropine		P. value
	Mean	SD	Mean	SD	
Baseline (before midazolam)	92.6	9.5	90.9	9.4	0.794
1 min after test dose	93.8	8.4	91.6	4.7	0.468
After intubation	97.5	9.7	99.3	10.7	0.589
5 min	90.1	6.7	89.5	9.9	0.361
10 min	88.6	9.6	86.9	8.6	0.653
15 min	89.6	7.5	88.6	9.1	0.872
20 min	89.6	8.5	89.4	6.9	0.919
25 min	89.3	9.0	88.5	8.1	0.706
30 min	91.6	7.5	88.4	10.3	0.438
35 min	90.8	9.4	89.5	8.6	0.881
40 min	88.2	10.6	87.0	9.4	0.681
45 min	90.5	7.0	88.5	7.5	0.561
50 min	88.5	8.7	88.4	8.9	0.765
55 min	90.0	9.8	89.6	7.9	0.544
60 min	89.2	7.0	89.6	9.7	0.766

Table 5. Comparison of diastolic blood pressure between both groups

	Glycopyrolate		Atropine		P. value
	Mean	SD	Mean	SD	
Baseline (before midazolam)	51.6	4.5	52.5	6.7	0.663
1 min after test dose	51.1	5.4	51.0	5.8	0.734
After intubation	58.8	7.9	57.7	6.9	0.571
5 min	52.6	6.5	52.7	5.8	0.823
10 min	50.4	9.4	52.7	8.8	0.661
15 min	49.1	5.7	51.3	7.6	0.545
20 min	50.0	8.6	50.4	8.1	0.613
25 min	50.2	6.8	50.0	6.3	0.772
30 min	50.2	5.7	51.0	7.5	0.598
35 min	51.0	7.0	50.1	6.2	0.678
40 min	50.3	8.6	50.8	6.9	0.867
45 min	52.7	5.8	51.6	7.6	0.661
50 min	51.2	7.5	50.1	6.9	0.801
55 min	50.8	5.5	50.6	5.7	0.741
60 min	51.8	4.9	50.3	7.7	0.679

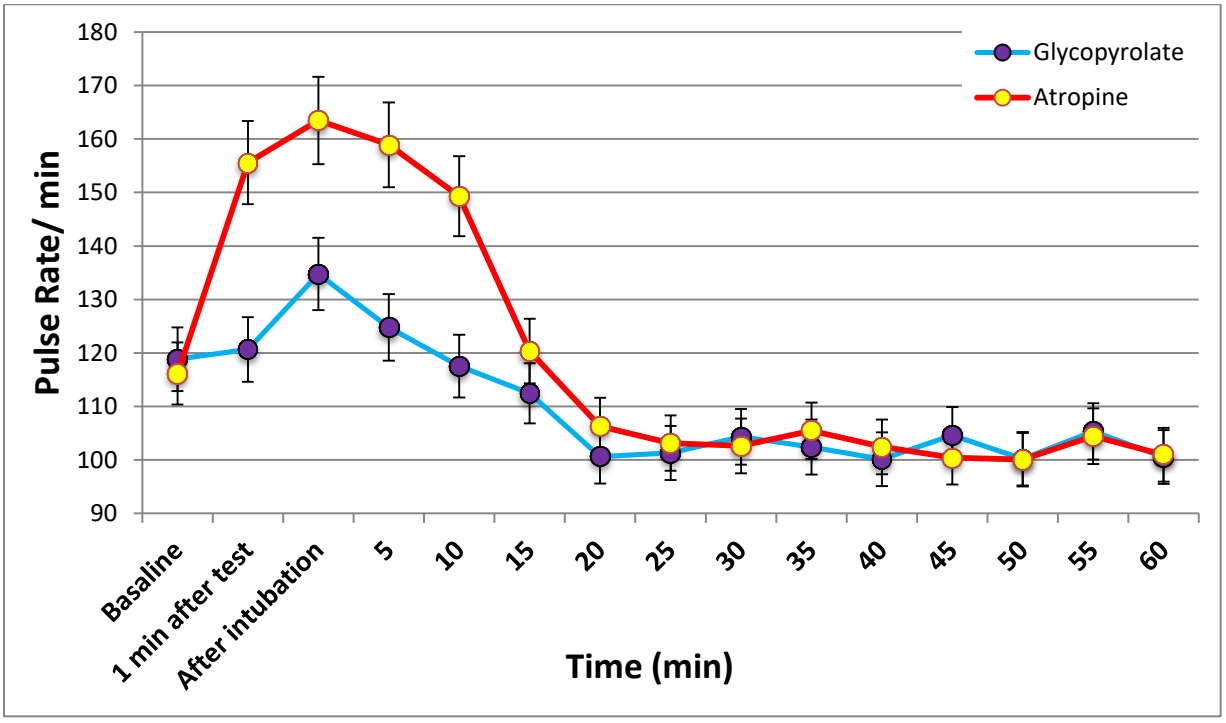

Figure 1. Timeline of pulse rate in both studied groups

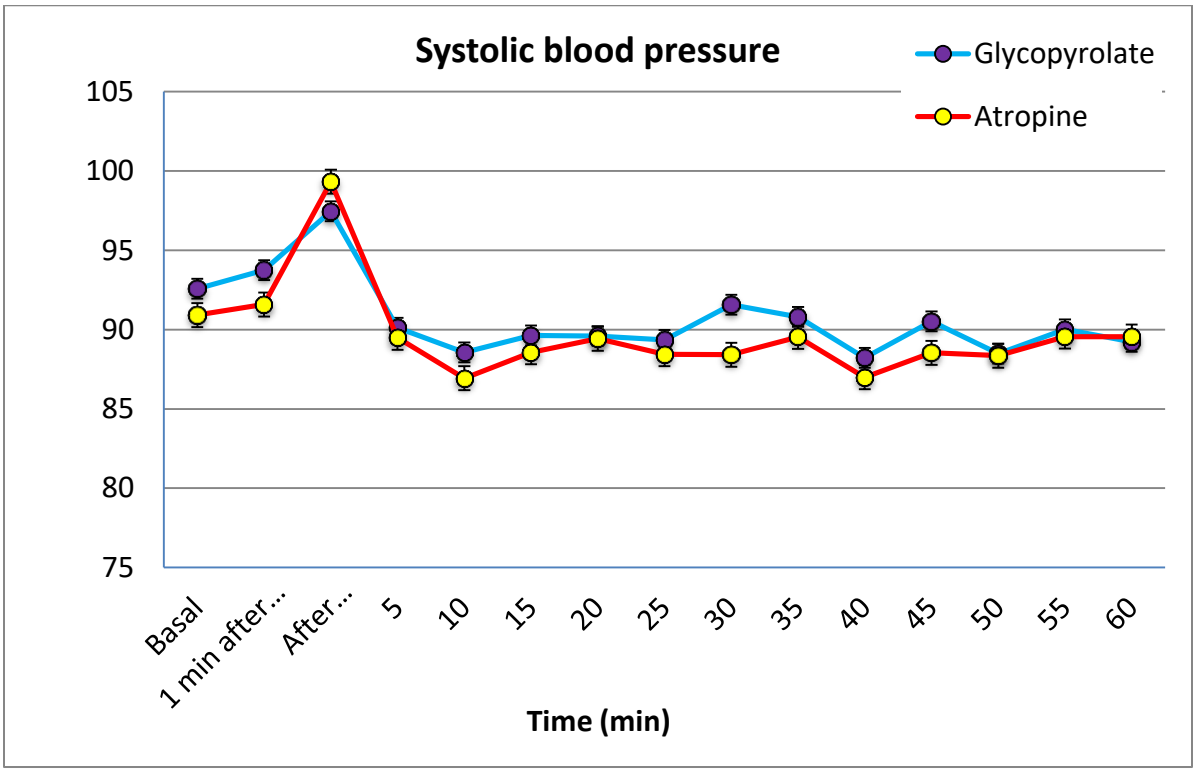

Figure 2. Timeline of systolic blood pressure in both groups

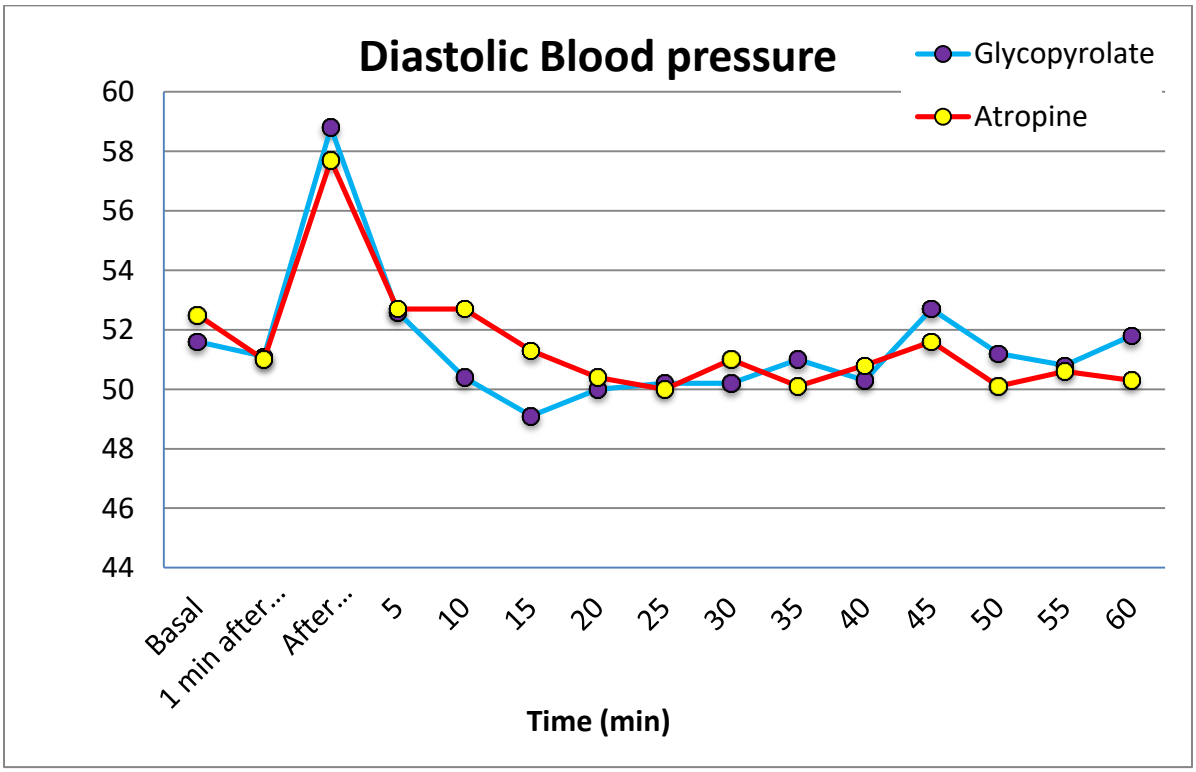

Figure 3. timeline of mean of diastolic blood pressure in both groups

4 DISCUSSION

Our study found that glycopyrrolate has more haemodynamic stability than atropine according to the pulse rate in the first 15 minutes. Both drugs have no effect on BP.

E. A Shipton et al show the effect of prmedication with intramuscular atropine and glycopyrrolate on the cardiovascular changes resulting from the performance of laryngoscopy and tracheal intubation has been evaluated in two groups of 25 patients undergoing surgery. Neither atropine nor glycopyrrolate attenuated the hypertensive and tachycardia response to laryngoscopy and intubation; both significantly enhanced it ($P < 0.05$) (14).

Desalu I, et al show the effectiveness of atropine and glycopyrrolate to provide cardiovascular stability on induction of anesthesia in children has been long debated. In their study, pediatric patients undergoing nitrous oxide, oxygen and halothane anesthesia were randomly divided in to two groups to ascertain whether atropine or glycopyrrolate would provide better stability. Atropine and glycopyrrolate provide equal cardiovascular stability in subjects from six months to 10 years of age, with greater stability in subjects under two years old as compared with those two to 10 years old (15).

P. Annila et al show the effect of anticholinergics on the incidence of cardiac arrhythmias during pediatric anesthesia. ASAI-II children (n=77) undergoing adenoidectomy were randomly allocated to three groups. Intravenous atropine was given in group A (n=25), glycopyrrolate in group G (n=27) and physiological saline in group P (n=25) 3 min before induction of anesthesia. Ventricular tachycardia occurred in 16.0%, 18.5% and 12.0% of the children in groups A, G and P respectively. The incidence of ventricular arrhythmias (ventricular tachycardia, ventricular bigeminy, ventricular premature beats) was 20.0% in grop A, 44.4%in group G and 36.0% in group P. Bradycardia (less 70 beats per min) was observed in 0.0%, 14.8% and 24.0% of patients in groups A, G and P respectively (A vs P, $P < 0.05$). The use of anticholinergics did not influence the incidence of ventricular arrhythmias during halothane anesthesia in children. Bradycardia was more common in the placebo group than in atropine group (16).

5 CONCLUSIONS

Patients who received Glycopyrrolate were more haemodynamic stable than those who received atropine regarding change in pulse rate in the first 15 minutes. We recommend to use glycopyrrolate as premdication in paediatric patients during anaesthesia as it cause less haemodynamic changes.

Ethical Issue:

All ethical issues were approved by the author and was taken from the scientific committee of the Iraqi Ministry of health . Participation in this research was voluntary and all the patients have signed the informed consent forms. Data collection was in accordance with Ethical Principles of Declaration of Helsinki of the world Medical Association, 2013, for research involving human subjects.

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