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K^{+ATP} CHANNELS MODULATE HAEMODYNAMICS, BIOCHEMICAL AND HEMATOLOGICAL AFTER PRETREATMENT WITH THE K (ATP) OPENER PINACIDIL AND PHOSPHOLIPASE C INHIBITOR ON ETOMIDATE IN THE MICE

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ABSTRACT

Etomidate intravenous anesthetics that are recognized to have minimal effects on clinically measured endpoints of cardiovascular function. Thus, they are often used as induction agents in patients with hemodynamic instability. K^{+}ATP channels are known to be activated by hyperpolarizing agonists, such as diazoxide, pinacidil, cromakalim, K^{+}ATP channel agonists are used as therapeutic agents in a variety of cardiovascular diseases, including essential hypertension, angina pectoris, myocardial ischemia, and cerebral vascular disease. This study was conducted to evaluate the effects of the potassium channel opener drug Pinacidil and Phospholipase C inhibitor, U73122 on Etomidate with K^{+}ATP channels opener drug modified the effects on blood pressure, heart rate and hematological parameters like the RBC, WBC, hemoglobin and serum alanine and aspartate amino-transferase enzymes in the mice.

KEYWORDS: ATP-sensitive potassium channel, Etomidate, Phospholipase C inhibitor, hemodynamic.

INTRODUCTION

Intravenous anesthetics Etomidate used to induce and maintain general anesthesia and to provide sedation during local and regional anesthesia. These agents can depress

cardiovascular function in humans[1-3] and animals.[4,5] The mechanisms underlying in vivo cardiovascular depression by intravenous anesthetics are not well understood but probably include a reduction in after load[6,7] and preload[8,9] and direct myocardial depression.[10,11] Although the mechanisms of intravenous anesthetic-induced negative inotropic effects appear to be diverse,[12] increasing evidence suggests that these agents exert direct negative inotropic actions in vivo and in vitro[13] Because changes in contractile force reflect an interaction between Calcium^{2+} influx and Potassium efflux through the sarcolemma, Calcium^{2+} release and sequestration by the sarcoplasmic reticulum, activity of membrane Calcium^{2+} and Potassium pumps, and the Calcium^{2+} sensitivity of the contractile proteins, it is possible that these agents may interfere with any one of these steps, thus decreasing contractility.

Although all intravenous anesthetics have negative inotropic effects, researchers frequently contend that Etomidate is the least potent. Preliminary studies implicate sarcolemmal ion channels as a potential site of intravenous anesthetic-induced negative inotropic action. Etomidate, an imidazole derivative, is potent hypnotic agent used for intravenous anaesthetic induction. It has stable hemodynamic profile, minimal respiratory side effects and no histamine release. It is very useful in hemodynamically compromised patients[14, 15]

The potassium channels are an important class of ionic channels, whose function is regulated by changes in the intracellular level of adenosine triphosphate (ATP) levels are elevated and open, when intracellular adenosine level decline, thus linking membrane potential to the metabolic state of the cell[16] opening them allows the passage of potassium ion out of the cell, causing trans membrane hyperpolarization and repolarization. These effects reduce intracellular calcium channels and inhibiting intracellular calcium release, resulting in smooth muscle relaxation[17] Opening of K^+ATP has been shown to play an important role in the vasodilatory action of antihypertensive drugs such as cromakalim pinacidil[18], dizoxide , and minodixil sulphate Same mechanism also contributes to the vasodialator action of nicorandil. Although many of these compounds may also open other types of channels, their primary mechanism of action, uncovered after the discovery of these drugs as hypotensive agents, is believed to involve opening of potassium channels, which cause membrane hyperpolarization, resulting in raising of the threshold for calcium entry through voltage sensitive calcium channels[19,20,21]

Adenophostin-A, a novel compound isolated from cultures of *Penicillium brevicompactum*, has been shown to stimulate Ca^{2+} release from inositol-1,4,5- trisphosphate (IP3)-sensitive

Ca^{2+} a stores in microsomal preparations, Permeabilized cells, and lipid vesicles containing purified IP3 receptor.[22-25] 4-Aminopyridine (4- AP) is an orphan drug indicated for the treatment of neuromuscular disorders.

There is a great controversy around the use of this drug because of its narrow safety index and because a large number of adverse effects have been reported. Moreover, it was shown to induce cell death in different cell lines, being reported mainly apoptosis and necrosis as the principal pathways of cell death mediated by blockage of K^+ channels or the Na, K-ATPase, but until now there are no *in vivo* studies on the anesthetic effects of Etomidate along with 4-aminipyridine pretreatment and subsequent changes on biochemical, haemodynamic parameters in the blood of mice.[26,27] In addition, U73122 the Phospholipase C inhibitor, which is thought to increase both basal and receptor-stimulated DAG levels, increases $[Ca2+]$ and whole-cell currents in cells over-expressing TRPC6 channel.[28,29]

The purpose of this study was to determine whether the pre-treatment of Etomidate with pinacidil or U73122 on hemodynamic and hematological changes modulate the effects on blood biochemical profile in mice.

MATERIALS AND METHODS

Environmental Temperature: The proper room temperature is essential for accurate blood pressure measurements and all biochemical studies. The room temperature was maintained at approximately 24- 26°C. Animals 48 Swiss Albino mice were included in the study in 7 groups of 6 animals in each (n=6). One another group served as a reserve animal group. Experiments were performed on either sex of Swiss albino mice (30–40g). Animals were procured from the animal house and maintained on a natural day–night cycle (12hr dark: 12hrs light) at room temperature of about 24-26°C, with free access to standard food pellets and water. Animals were acclimatized for at least seven days before exposure to experiments. Experiments were carried out between 10:00-17:00 hours. The animals were obtained from central animal house of JKKMMRFs, Namakkal. All the experimental procedures and protocols were viewed and approved by the Institutional Animal Ethics Committee (IAEC) of the institute.(Registration No JKKMMRFCP/ IAEC/ 2012/ 014).

Chemicals and drugs

Etomidate, was purchased from Rablon healthcare, (Mumbai, India), Pinacidil were obtained from Ultra-Tech Speciality Chemicals Pvt. Ltd. (Mumbai, Maharashtra, India). U73122 was

purchased from Pro Lab Marketing Pvt. Ltd, (New Delhi, India). Adenophastin A was bought from Merck Millipore India. Pvt. Ltd. (Bangalore, Karnataka, India) Soluble Sterile Water follow reconstitution),4-Aminopyridine obtained from 4-AP, BI Biotech India pvt. Ltd,(New Delhi, India). 4-Aminopyridine Soluble in water to 100 mM, peptide solutions.U73122 Soluble to 100 mM in DMSO and to 100 mM in ethanol Stock solutions in DMSO. Sterile water for injection was obtained from Nirmal Prime Health Care (Mumbai, India).

Blood Pressure Evaluation

The non-invasive blood pressure methodology consists of utilizing tail-cuff placed on the tail to occlude the blood flow [30]. Upon deflation, one of non-invasive blood pressure sensors, placed distal to the occlusion cuff, can be utilized to monitor the blood pressure. Volume Pressure Recording (VPR) as provided by Kent scientific corporation (USA). The Volume Pressure Recording sensor utilizes a specially designed differential pressure transducer to non-invasively measure the blood volume in the tail. Volume Pressure Recording can actually measure six blood pressure parameters simultaneously including for e.g systolic blood pressure, diastolic blood pressure, heart rate**.**

Estimation SBP, DBP and HR

The CODA tail-cuff system uses Volume Pressure Recording to evaluate blood pressure by assess the tail blood volume. These systems provide with capacity of different blood pressure parameters include systolic and diastolic blood pressure, heart rate, Measurements can be made on anesthetized mice. After end of the last cycle the received cycles will be automatically displayed in spreadsheet format within the system application. Data are in the Excel file. A common practice is to obtain the Mean and SEM.

Blood sampling method and sample handling

All animals were un fasted and samples were collected in the afternoon. Blood for hematology was collected into Microtainer Brand Tubes with EDTA used as an anticoagulant (Pattabhis, Mumbai). Blood for serum biochemistry analysis was collected into preservative-free serum separating gel for blood collection tube, Microtainer Brand Serum Separator Tubes (Pattabhis, Mumbai). For all collection techniques, the stopper from the tube was removed and blood was deposited directly from the syringe after removal of the needle or directly by dripping into the tube. The blood for serum biochemistry evaluation was allowed to clot at room temperature and was centrifuged for 10 min using an Remi centrifuge (Universe Sugical Equipment Co, Chennai, Tamilnadu), and the serum was separated.[31,32]

All samples were processed in the same manner serum biochemistries was conducted were measured using an auto humalyser (Auto humalyser 900S plus Human, Germany) [33] and included Alanine amino transferase (ALT), Aspartate amino transferase (AST), Creatinine, Hematological parameters, such as red blood cell (RBC), white blood cell (WBC), The serum content of hemoglobin (HB), Hematological analysis for (RBC, WBC, HB, PLT) were estimated using a hematology analyzer (Sysmex KX-21N Auto Hematology Analyzer, KOBE, JAPAN).[34] Electrolyte analyzer have use the ion selective electrode, Sodium (Na+) Potassium (K+) and Calcium ions (Ca2+) the analysis of the samples was conducted by (9180 Electrolyte Analyzer, Roche, Germany).

Hematological analysis for White Blood Cell count, Red Blood Cell count, Platelet Count, Hemoglobin

We use the blood from cardiac puncture for mostly haematological assays so we collect the blood in EDTA-coated which is more suitable for haematological downstream application. Buy pre-coated sample tubes but just add 10% 0.5M sterile EDTA of the expected blood volume (so 100□l) into a 2ml tube. Just before the puncture draw this up in a syringe with the needle are using for the puncture, pull the plunger all the way back to coat the syringe and push the EDTA back into the tube. Whatever is left in needle and syringe will be enough to prevent clotting. We perform this procedure under terminal an aesthesia. Rest of the mice on its back with its nose in a tube connected to the isoflurane device used medium gauge seized needles; insert the needle under aspiration under the sternum pointed slightly towards the left side. Blood remove the needle before you the tube to prevent rupture of blood cells by sheering forces. Hematological analysis for WBC, RBC, PLT, and Hb were made using a hematology analyzer.

Biochemical analysis for Aspartate aminotransferase, Alanine aminotransferase, Creatinine

Blood samples were obtained from retro orbital venous sinus in lithium heparin tubes. Sera were obtained by centrifugation and were collected in plain tubes stored at -20ºC for analysis. The mice were randomly divided into six groups with each group consisting of six mice. Biochemical Analysis for AST, ALT, and CRT was made using Sodium, Potassium, and Calcium ions were determined by an electrolyte analyzer.

Statistical Analysis

Data was represented in Mean ± SEM. Paired sample t-test was used for comparison between pre anesthetic treatment and post anesthetic treatment measurements by using one-way analysis of variance (ANOVA).

Grouping: Treatment Groups are divide as following.

Groups	Treatment
Group -I	Solvent control (Sodium chloride alone (0.9%),(5 ml/kg, i.p)
Group -II	Test drug (Etomidate, (5 mg/kg, i.p),
Group -III	Pretreated with potassium channels opener and Test drug(pinacidil,5-25 microgram, i.c.v. + Etomidate)
Group -IV	Pretreated with Phospholipase C inhibitor along with test drug (U73122 10 µmol/kg, (i.v), + Etomidate)
Group -V	Pre treated with th IP3 agonists Adenophastin A (2.5 µM, i.p), with Etomidate)
Group -VI	Pretreated with potassium channel blocker With test dose(4 Aminopyridine (1.5 mg/kg,i.p) + Etomidate)

OBSERVATIONS

The purpose of this study was to determine whether the pre-anesthetic treatment and post-anesthetic treatment effects on Etomidate with Pinacidil or U73122 mediate biochemical and hematological changes and the effect on blood profile in mice. The impact of the anesthetic with Potassium channel opener Pinacidil may suppress or induced anesthetic action of Etomidate. The blood for serum biochemistry evaluation included Alanine amino transferase (ALT), Aspartate aminotransferase (AST), Creatinine, and hematological parameters, such as red blood cell (RBC), white blood cell (WBC), The serum content of hemoglobin,(HB),Platelets, blood Electrolytes like the (Na^{+}),(K^{+}),(Ca^{2+}), The non-invasive blood pressure (SBP, DBP, and HR) Variables were taken before pre-anesthesia induction 30 minutes after post-induction and then at 20- minute intervals. All the results are depicted in Tables 1 to 5.

Table 1: Hematological, hemodynamic and biochemistry parameters in Etomidate.

Test drug only Etomidate					
Parameters	**Normal Value**	**Pre-Induction Mean±SEM**	**Post-Induction Mean±SEM**	**95%CI**	
				Lower	**Upper**
VITAL SIGN:					
SBP (mmHg)	120	121.14±4.16***	118.13±1.36	110.44	131.84
DBP (mmHg)	71	70.42±3.28***	68.26±1.34	61.98	78.53
HR (bpm)	650–750	736.10±1.23*	723.34±2.18	732.94	739.76
HEMATOLOGY:					
RBC ($x10^{12}$/ l)	7.2-10.1	8.94±2.26**	9.22±4.12	3.13	14.75
WBC (x 10^9/ l)	10.2-13.8	12.2±5.21**	13.8±2.28	-1.19	25.59
Hb (gm %)	0.36-13.7	13.4±6.82**	13.4±2.33	-4.13	3.93
PLATELETS (x 10^9 / l)	385-610	513.6±4.4*	498.8±1.46	502.29	524.91
BIOCHEMICAL:					
ALT (IU/L)	40-94	90.66±3.22***	88.14±2.44	82.38	98.93
AST (IU/L)	150-225	222.14±2.14***	211.13±2.28	216.64	227.64
CREATININE (mg/dl)	0.8-1.4	1.2±3.33***	1.3±2.58	-7.36	9.76
Na^+(mM/L)	127-165	168.26±4.58**	163.46±03.16	156.48	180.04
K^+ (mM/L)	3.2-6.8	7.44±1.22**	6.8±2.46	4.3	10.57
Ca^+(mM/L)	2.5-4.0	4.2±5.33**	4.0±1.48	-9.5	17.9

Test Dose Etomidate Statistical analysis of parametric data significant level P values*P < 0.05; statistically significant **P < 0.01; significant ***P < 0.001.

Table 2: Effects of Pretreated Pinacidil with Etomidate treatment on hematological, Biochemical and Vital signs, parameters of mice.

Pretreated Pinacidil with Etomidate					
Parameters	**Normal Value**	**Pre-Induction Mean±SEM**	**Post-Induction Mean±SEM**	**95% CI**	
				Lower	**Upper**
VITAL SIGN:					
SBP (mmHg)	120	124.28±2.76**	120.16±3.12	117.18	131.38
DBP (mmHg)	71	76.36±1.48**	71.18±4.18	72.55	80.16
HR (bpm)	650 – 750	776.46±2.42*	748.13±4.22	770.24	782.68
HEMATOLOGY:					
RBC (x 10^{12}/ l)	7.2-10.1	10.81±2.18***	10.2±1.34	5.2	16.41
WBC(x 10^9/ l)	10.2-13.8	14.64±0.43***	13.8±1.49	13.53	15.74
Hb (gm %)	0.36-13.7	14.38±1.21***	13.2±1.88	11.26	17.49
PLATELETS (x 10^9 / l)	385-610	618.48±22.46*	610.18±10.84	560.74	676.22
BIOCHEMICAL:					
ALT (IU/L)	40-94	98.56±2.33**	92.56±2.52	92.57	104.55
AST (IU/L)	150-225	231.12±4.16**	220.53±4.68	220.42	241.82
CREATININE (mg/dl)	0.8-1.4	1.7±1.28***	2.15±1.47	-1.59	4.99
Na^+(mM/L)	127-165	156.82±08.46***	152.42±0.86	135.07	178.57
K^+(mM/L)	3.2-6.8	7.0±0.14***	6.9±1.28	6.64	7.36
Ca^+(mM/L)	2.5-4.0	4.2±0.26***	4.0±1.28	3.69	4.71

Table 3: Pretreated U73122 with Etomidate at different drug groups.

Pretreated U73122 With Etomidate					
Parameters	**Normal Value**	**Pre-Induction Mean±SEM**	**Post-Induction Mean±SEM**	**95% CI**	
				Lower	**Upper**
VITAL SIGN:					
SBP (mmHg)	120	130.66±4.24**	126.32±4.84	126.21	135.11
DBP (mmHg)	71	76.82±1.04**	73.41±2.26	75.72	77.91
HR (bpm)	650 – 750	776.45±1.92*	759.33±1.23	774.43	778.437
HEMATOLOGY:					
RBC (x 10^{12}/ l)	7.2-10.1	10.8±1.42***	10.2±2.44	9.31	12.29
WBC(x 10^{9}/ l)	10.2-13.8	14.8±2.88***	14.2±2.24	11.77	17.82
Hb (gm %)	0.36-13.7	14.6±1.28***	14.0±2.28	13.25	15.97
PLATELETS (x 10^{9} / l)	385-610	630.12±4.02*	622.48±0.84	625.9	634.34
BIOCHEMICAL:					
ALT (IU/L)	40-94	98.56±1.33**	93.43±1.52	97.16	99.95
AST (IU/L)	150-225	242.12±4.16*	229.53±3.68	237.75	246.49
CREATININE (mg/dl)	0.8-1.4	1.86±0.48***	1.40.15±1.47	1.35	2.36
Na^{+}(mM/L)	127-165	174.61±8.12*	166.24±0.88	166.09	183.13
K^{+}(mM/L)	3.2-6.8	7.2±1.48***	6.6±1.02	5.64	8.75
Ca^{+}(mM/L)	2.5-4.0	4.4±1.08***	4.0±1.06	3.26	5.53

Mice Pretreated with PLC Inhibitor U 73122 with Etomidate. Statistical analysis of parametric data (Pre-induction and Post-induction) was performed using one-way analysis of variance (ANOVA).

Table 4: Pretreated Adenophastin A with Etomidate Pre and post anesthesia blood variables in mice.

Pretreated Adenophastin A with Etomidate					
Parameters	**Normal Value**	**Pre-Induction Mean±SEM**	**Post-Induction Mean±SEM**	**95% CI**	
				Lower	**Upper**
VITAL SIGN:					
SBP (mmHg)	120	108.26±4.12*	114.40± 2.82	103.94	112.58
DBP (mmHg)	71	60.86±2.08*	68.26±2.46	58.67	63.04
HR (bpm)	650 – 750	624.68±4.74*	648.16±0.28	619.7	629.66
HEMATOLOGY:					
RBC(x 10^{12}/ l)	7.2-10.1	10.8±1.24***	09.18±2.18	9.49	12.1
WBC (x10^{9}/ l)	10.2-13.8	15.1±1.04**	14.0±1.14	14	16.19
Hb (gm %)	0.36-13.7	14.6±0.68***	13.4±0.12	13.88	618.15
PLATELETS (x 10^{9} / l)	385-610	616.22±2.22**	608.42±0.64	613.89	666.22
BIOCHEMICAL:					
ALT (IU/L)	40-94	96.12±1.09**	94.28±2.78	94.97	97.26
AST (IU/L)	150-225	244.12±2.64*	232.72±6.38	241.35	246.89
CREATININE (mg/dl)	0.8-1.4	1.87±0.43***	1.4.26±3.63	1.41	2.32
Na^{+}(mM/L)	127-165	172.08±9.32**	166.28±10.82	162.3	181.86
K^{+}(mM/L)	3.2-6.8	7.4±0.32 ***	136±-2.88	7.06	7.73
Ca^{+}(mM/L)	2.5-4.0	4.2±0.86 ***	4.0±-0.84	3.29	5.1

Pretreated With Adenophastin A Etomidate Values are expressed as mean ± SEM for Six animals (N=6) in each group.

Table 5: Clinical biochemistry, Vital signs, and hematological profile parameters in mice Pretreated 4-Aminopyridine with Etomidate.

Pretreated 4 Aminopyridine with Etomidate					
Parameters	**Normal Value**	**Pre-Induction Mean±SEM**	**Post-Induction Mean±SEM**	**95% CI**	
				Lower	**Upper**
VITAL SIGN:					
SBP (mmHg)	120	94.16±2.88*	108.14± 1.60	91.13	97.18
DBP (mmHg)	71	62.16±1.72**	68.16±1.06	60.35	63.95
HR (bpm)	650 – 750	610.18±1.14*	632.66±1.74	608.98	611.38
HEMATOLOGY:					
RBC (x 10^{12}/ l)	7.2-10.1	11.66±1.64***	10.4±2.18	9.93	13.38
WBC (x 10^{9}/ l)	10.2-13.8	14.84±2.06***	13.4±0.34	12.67	17.2
Hb (gm %)	0.36-13.7	15.0±1.02**	14.2±2.46	13.92	16.07
PLATELETS (x 10^{9} / l)	385-610	608.12±3.46***	624.12±3.12	604.49	611.75
BIOCHEMICAL:					
ALT (IU/L)	40-94	98.16±4.03**	93.43±1.52	93.93	102.39
AST (IU/L)	150-225	248.02±0.16*	239.14±3.16	247.85	248.19
CREATININE (mg/dl)	0.8-1.4	2.02±0.26***	1.40.15±2.27	1.74	2.29
Na^{+}(mM/L)	127-165	174.01±0.16*	162.31±0.24	173.84	174.18
K^{+}(mM/L)	3.2-6.8	7.28±2.82***	6.34±1.42	4.32	10.24
Ca^{+}(mM/L)	2.5-4.0	4.8±1.18***	4.2±1.46	3.56	6.03

Animal's pretreated 4-Aminopyridine with Etomidate.Significant level P values*P < 0.05; statistically significantP < 0.01; significant ***P < 0.001. Statistically highly significant**

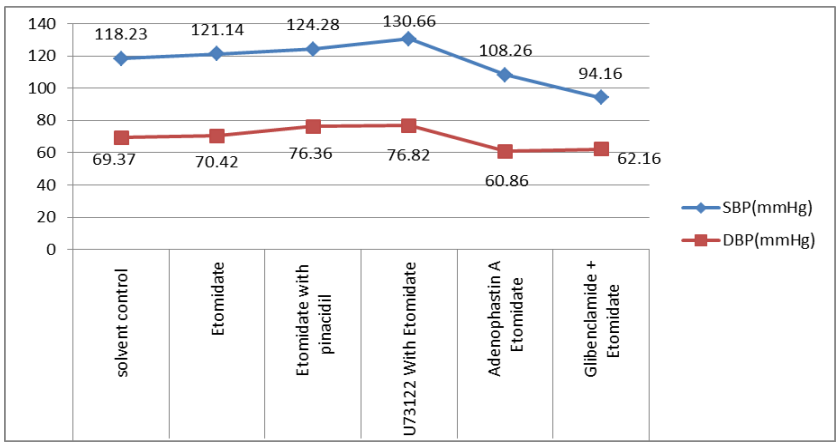

Fig. 1: Comparison of Hemodynamic parametersin Etomidate with different groups on mice (Mean±SEM pre-and post treatment Systolic and Diastolic blood pressure Expressed (mmHg: millimeter of mercury).

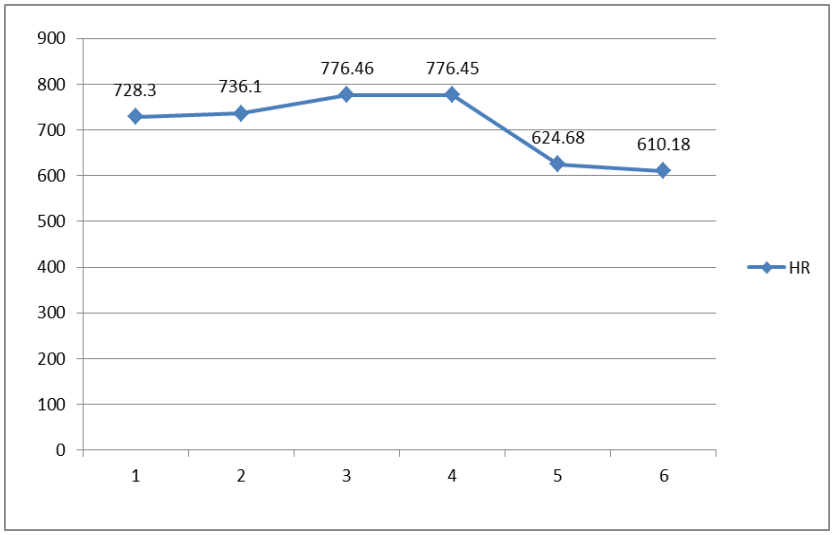

Fig. 2: Mean Heart Rate evolution in different groups with Etomidate Pre-and post treatment heart rates expressed (bpm: breaths per minute).

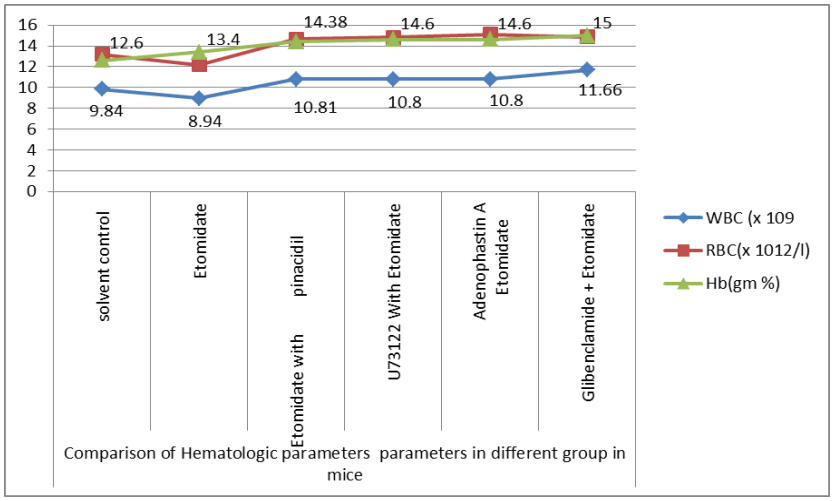

Fig. 3: Hematological RBC, WBC, HB, levels On Etomidate.

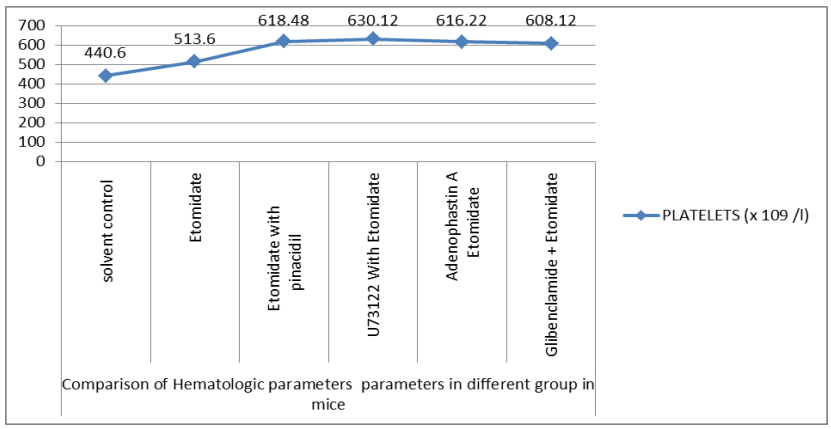

Fig. 4: Platelets levels Etomidate with Different Drug Groups.Platelet counts are expressed X 10^9 per liter of Mice. * Significantl (P< 0.05) different drug groups.

RESULTS AND DISCUSSION

Effects of Hemodynamic, Hematological &Biochemical Changes on Etomidate in the mice

Monitoring of etomidate induction agent, heart rate, systolic, diastolic blood pressure were compare with baseline readings. Etomidate treated alone did not any significant changes in hemodynamic parameters (121.14±4.16). Were administered with potassium channel activator pinacidil statistically significant increased HR, SBP, and DBP (124.28±2.76). The impact of the anesthetic with Potassium channel opener pinacidil may induce anesthetic action of Etomidate. Phospholipase C inhibitor U73122, with etomidate (130.66±4.24) exerted significant increase effects on HR, SBP, and DBP in mice. Adenophastin is the most potent agonist at the inositol 1, 4, 5-trisphosphate receptor treated there was a decline from the baseline in heart rate (624.68±4.74), systolic, diastolic pressure (108.26±4.12), (60.86±2.08), Pretreated with 4-aminopyridine with Etomidate significant decrease from the baseline control in heart rate (610.18±1.14), systolic, diastolic pressure (94.16±2.88), (62.16±1.72), (Table 1, figure 1).

Effects of Haematology parameters Changes on Etomidate in the mice

The results of are summarized in Table 1, there were differences on etomidate in haematology there was no significant increase in RBC, WBC, Hb, Platelets while etomidate treated alone. Pinacidil a potassium channel activator pretreated with etomidate with there was significant increase in RBC, (10.81±2.18), WBC (14.64±0.43), Hb (14.38±1.21), Platelets (618.48±22.46). Phospholipase C U73122, with etomidate significant increase in RBC (14.8±2.88), WBC (10.8±1.42), Hb (14.6±1.28), and platelets (630.12±4.02). Induced hematological parameters in mice and significant increase in Adenophastin administrated with Etomidate. K^+ channel blocker 4-aminopyridine induces the RBC, WBC, Hb, Platelets in mice

Serum Biochemistry Values on Etomidate

As shown in the table 1 pretreated with PLC inhibitor U73122 there was significant increase in Na^+, K^+ Ca^+. While treated with etomidate. Induced ALT (96.12±1.09), AST (244.12±2.64), Creatinine (1.87±0.43). Adenophastin and 4-Aminopyridine treated with etomidate induced Serum Biochemistry levels ALT, AST, Creatinine, Na^+, K^+, and Ca^+ in mice.

Summary

General anesthetic induction agents may decrease arterial blood pressure via myocardial depression, vasodilatation and attenuation of autonomic nervous activity. We compared the hemodynamic responses induction agents' etomidate alone and various other groups like ATP sensitive channel Opener Pinacidil and Phospholipase-C U73122 Inhibitor after studying the hemodynamic effects of an induction dose of etomidate was associated with significant decreases in SBP and DBP. Examined the effect of propofol leading myocardial function by measuring changes in left ventricle function via transthoracic tissue decrease cardiac filling or a effect of a through negative inotropic action of etomidate.

The results of our study Table 1-5, propose that Changes in HR, SBP, and DBP monitoring of Etomidate induction agents. Heart rate, systolic and diastolic blood pressure and baseline control readings were recorded. Etomidate treated alone not any significant changes in hemodynamic parameters (121.14±4.16). This study reveals that at the hemodynamic variations with etomidate were less than propofol throughout the period induction.Pinacidil is an antihypertensive drug, stimulate vasodilatation affects both small and large arteries and leads in normotensive subjects to a slight decrease in blood pressure. Previous studies shows that Pinacidil treated alone decrease the hemodynamic such as BP, and HR.

In this study Changes in HR, SBP, and DBP monitoring of Pretreatment of Pinacidil with Etomidate, significant increased HR, SBP, and DBP. The impact of the anesthetic with Potassium channel opener Pinacidil may induce anesthetic action of Etomidate. Phospholipase C U73122, with etomidate (130.66±4.24) exerted significant increase effects on HR, SBP, and DBP in mice. Inositol tri-phosphate are stimulated via phospolipid metabolism and the release of IP_3 channels Adenophastin A affect Etomidate anesthesia. Influence of intracellular Ca^{2+} release to increase cytosolic Ca^{2+} levels during the activation of endoplasmic membrane ion channels. The IP_3 agonist Adenophastin A modulated the anesthetic effects of etomidate decrease from the baseline in heart rate (624.68±4.74), systolic, diastolic pressure (108.26±4.12, 60.86±2.08).

Pretreated with 4-AP, K^+ channel blocker treated with Etomidate did not influence systolic pressure in conscious normotensive or spontaneous hypertensive Mice, although 4-AP, at the dose was reported to reduce the systolic pressure in anesthetized renal hypertensive mice, suggesting that conscious mice keep intact reflex to offset the effect of 4-AP, on systolic

pressure. Heart rate (610.18±1.14), systolic, diastolic pressure, reduced when compared to its control.

Blood profile on Etomidate in mice

Etomidate treated alone not any significant changes in hemodynamic parametersin this study reveals that at the hemodynamic variations with Etomidate were less than Propofol throughout the period induction. Previous studies shows that Pinacidil treated alone decrease the blood pressure and heart rate. Our experimental study shows that phospholipase C Inhibitor-U73122 with etomidate exerted significant increase effects on HR, SBP, and DBP in mice. The IP_3 agonist adenophastin a modulated the anesthetic effects of etomidate significant reduce from the baseline control in HR, SBP, and DBP. Pretreated 4-aminopyridine treated with Etomidate significant decline from the baseline in heart rate, systolic, diastolic pressure in these mice.

Haematology Parameters on Etomidate there was no significant increase in RBC, WBC, Hb, and Platelets while etomidate treated with alone. Pretreated with Pinacidil with etomidate there was significant increase in RBC, WBC, Hb, and Platelets. Phospholipase C - U73122, with etomidate significant increase in RBC, WBC, Hb, and Platelets. Induced Hematological parameters significant increase in Adenophastin administrated with Etomidate and also K^+ channel blocker pretreated 4-aminopyridine with Etomidate in mice induces level of the RBC, WBC, Hb, and Platelets.Serum Biochemistry Parameters on Etomidate significant increase in Na^+,K^+ Ca^+. While treated with Etomidate administrated with PLC inhibitor U73122 in mice Induced ALT, AST, and Creatinine. Pretreated 4-Aminopyridine, Adenophastin administered with Etomidate, Enhance the Serum Biochemistry levels in ALT, AST, Creatinine, Na^+, K^+, and Ca^+ in mice.

CONCLUSION

Etomidate produces only minimal effects on cardiovascular dynamics and therefore is widely recommended for patients with compromised cardiac function and hypotension. Despite the tremendous interest and considerable scientific progress in potassium channel openers over the past few years, the clinical benefit of many types of these agents has yet to proven. The ever present need for potassium channel selectivity and target validation remains a key hurdle. Without doubt, the most established potassium channel openers in the clinic area. Intravenous anesthetic agents and potassium channel activators on concurrent administration, K^+ channel begin the production of cGMP in the polarized and depolarized muscle tissues. This study propose with the aim of caring dealings of intravenous anesthetics on voltage

dependent K^+ in progress may support to create clear mechanisms basic anesthetic drug effect, These actions require support the research.

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