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Research Article

EFFECTS ON HAEMODYNAMICS, BIOCHEMICAL AND HEMATOLOGICAL CHANGES AFTER PRETREATMENT WITH THE KCNQ OPENER RETIGABINE AND DIACYGLYCEROL LIPASE INHIBITOR ON PROPOFOL IN THE MICE

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ABSTRACT

The mechanisms of action of general anesthetics are still being unraveled. Retigabine is a KCNQ/Kv7 channel opener and has potential therapeutic importance for epilepsy. On the other hand, Propofol an inducing general anesthetic drug may modulate the ATP sensitive channels according to recent reports. This study was conducted to evaluate the effects of the KCNQ potassium channel opener drug retigabine and DAG lipase inhibitor, RHC 80267 on propofol mediated effects on blood pressure, heart rate and hematological parameters like the RBC, WBC, hemoglobin and serum transaminase enzymes in the mice.

Key words: Retigabine, Propofol, Potassium channel, blood pressure, creatinine

INTRODUCTION

Anesthesia is an indispensable pre-requisite to most of the surgical interventions, both in humans and animals, so that the surgeon can perform surgical intervention with maximum precision and sagacity. General anesthetic must be capable of smooth induction and maintain optimum analgesia and skeletal muscle relaxation. Ion channels have been under intensive scrutiny for the possible role in the mechanism of General anesthetics. Potassium channels play a major role in controlling membrane excitability and thus represent interesting drug targets for the treatment of epilepsy and neuropathic pain. [1-3]. There are potassium (K^+) channel proteins that are widely distributed in the brain, inner ear, heart, pancreas, lung, and placenta[4-8]. Retigabine a voltage-dependent KCNQ K^+ channel (Kv.7) opener, exerts anticonvulsant and analgesic actions in the central nervous system[9-11]. Retigabine also has anti-nociceptive effects in rat models of persistent and chronic pain. The anti-nociceptive effects associated with retigabine administration were reversed by co-administration of KCNQ blockers [10-11]. Retigabine is a structural analog of the analgesic flupirtine and has shown activity in a wide range of animal models of epilepsy i.e chemically and electrically induced convulsions, kindling models of partial epilepsy, models of absence, genetically seizure-prone rodents thus thought to indicate a broad spectrum of anti-seizure activity [12-13].

On the other hand the anesthetic drug, propofol is a unique non-barbiturate, non-steroid, short-acting general intravenous anaesthetic agent [14]. Anaesthetic stage duration of propofol could be enhanced if used in combination with potassium channels openers like the Retigabine. Propofol, 2, 6 diisopropylphenol, is also known as Diprivan, an intravenous anaesthetic agent. Due to its fast induction and recovery time, it is widely used in daily clinical practice in surgical patients for the induction and maintenance of general anaesthesia [15, 16]. 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 (IP_3)-sensitive C^{2+} a stores in microsomal preparations, permeabilized cells, and lipid vesicles containing purified IP_3 receptor.[17-20]. 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.

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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 it was not described *in vitro* anesthetic effects of Propofol induced by 4-aminipyridine. Changes of biochemical and blood electrolytes, haemodynamic parameters in the blood profile in mice [21, 22].RHC80267 the DAG lipase inhibitor, which is thought to increase both basal and receptor-stimulated DAG levels, increases [Ca^{2+}] and whole-cell currents in cells over-expressing TRPC6 channel[23,24] .

However, when Propofol is used as an anaesthetic agent, various components of blood fluctuate more or less as compared to other intravenous anaesthetic agents [25, 26]. Many studies documented the adverse effects of Propofol on haemodynamics and blood profile of patients. For instance, Claeys *et al.* [27] reported a decrease in systolic and diastolic arterial pressure, even when a single dose of Propofol was given to the patient. Moreover it has a major impact on platelet aggregation along with effects on level of Alanine Amino transferase (ALT), Aspartate Amino transferase (AST), as well as Blood Pressure and Heart beat rate affected by the use of Propofol in surgery patients [28,29]. However some studies are available, which partially discussed the Propofol after effects on haemodynamics activity [30]. The purpose of this study was to determine whether the pre-treatment of Propofol with Retigabine or RHC 80267 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 8 groups of 6 animals in each (n=6). 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.

Chemicals & drugs

All standard chemicals and reagents were used in this study were of analytical grade. Methohexital for injection, (Indiamart **New Delhi, India**) Propofol (Taj Pharmaceuticals Ltd. Maharashtra, India), Retigabine (Glaxo Smith Kline, Mumbai, India), RHC 80267 (Cayman Chemicals, Mumbai,India) RHC 80267 made soluble in 100 mM in DMSO and to 100 mM in ethanol, 4- Aminopyridine((4-AP, **BI Biotech India PVT. Ltd. New Delhi, India)** 4- Aminopyridine made soluble in water to 100mM.

Blood Pressure Evaluation

The non-invasive blood pressure methodology consists of utilizing tail-cuff placed on the tail to occlude the blood flow [31]. 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 (n=6) blood pressure parameters simultaneously including for e.g systolic blood pressure, diastolic blood pressure, heart rate.

Blood sampling method and sample handling

All animals were unfasted 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 (IC) after removal of the needle or directly by dripping into the tube (RO. 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 [32,33]. All samples were processed in the same manner serum biochemistries was conducted were measured using an auto humalyser (Autohumalyser900Splus Human, Germany)[34].and included alanine aminotransferase (ALT), aspartate aminotransferase (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-21NAuto Hematology Analyzer, KOBE, JAPAN)[35]. Electrolyte analyzer have use the ion selective electrode, Sodium (Na^+) Potassium (K^+) and Calcium ions (Ca^{2+}) the analysis of the samples was conducted by (9180 Electrolyte Analyzer, Roche, Germany).

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 divided as following:

Groups	Treatment Group
Group I	Solvent control (Sodium chloride alone (0.9%),
Group II	Referance control (Methohexital 30 mg/kg i.v) [36].
Group III	Test drug (Propofol 12-26 mg/kg (i.v) [36].
Group IV	Pretreated with potassium channels opener and Test drug (Retigabine(0.1-10µm i.p).+ (Propofol 12-26mg/kg (i.v).
Group V	Pretreated with DAG lipase inhibitor along with test drug DAG lipase inhibitor (RHC 80267(1.3-2.6 µmol/kg i.v) .+ (Propofol, 12-26 mg/kg (i.v)
Group VI	Pretreated with DAG lipase inhibitor with potassium channels opener (RHC 80267, (1.3-2.6 µmol/kg i.v)+ (Retigabine(0.1-10µm i.p).
Group VII	Pretreated with potassium channel blocker With test dose of Propofol. 4- Aminopyridine(1.5 mg/kg s.c) + (Propofol 12-26mg/kg i.v)

OBSERVATIONS AND RESULTS

The purpose of this study was to determine whether the pre-anesthetic treatment and post- anesthetic treatment effects on Propofol with Retigabine or RHC 80267 mediate Biochemical and hematological changes and the effect on blood profile in mice. The impact of the anesthetic with Potassium channel opener retigabine may suppress or induced anesthetic action of Propofol. The blood for serum biochemistry evaluation included alanine aminotransferase (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 7

Table1: Comparison of Mean ± SEM of pre and post anesthesia blood sample values along with the level of significance (n=6). Vital signs, Serum biochemistry, Hematologic parameters in mice-Solvent Control 0.9%.

	Parameters	95%Confidence interval of Mean±SE the Difference			
		Pre-Induction Mean±SE	**Post-Induction Mean±SE**	**Lower**	**Upper**
SOLVENT CONTROL-GROUP -I	**VITAL SIGN:**				
	SBP(mmHg)	122.13±1.34*	120.16±1.22	118.68	123.3
	DBP(mmHg)	70.14±2.34	68.14±1.8	64.12	72.76
	HR(bpm)	680.28±1.77	660.18±1.44	675.73	663.88
	HEMATOLOGY:				
	RBC(x 10^{12}/l)	8.60±2.62*	8.2±2.1	1.86	13.59
	WBC (x 10^{9}	12.4±3.8	11.8±1.18	2.63	14.83
	Hb(gm %)	10.2±1.2	9.8±2.33	7.11	15.79
	PLATELETS (x 10^{9} /l)	390.3±6.3	372.3±1.44	374.1	376
	BIOCHEMICAL:				
	ALT (IU/L)	74.26±13.20**	68.14±4.33	40.32	79.27
	AST (IU/L)	180.13±4.82	172.13±3.68	164.67	181.59
	CREATININE(mg/dl)	1.2±0.66	0.8±0.11	- - 0.49	1.08
	Na+(mM/L)	140.18±0.89**	128.14±11.2	137.89	156.94
	K+(mM/L)	4.2±1.11	3.8±0.88	1.34	6.06
	Ca(mM/L)	3.2±0.22	3.1±1.24	2.63	6.28

The results of haematological and biochemical parameters recorded in group I animals and statistical analysis of parametric data (Pre-induction and Post-induction compared) was performed using one-way analysis of variance (ANOVA) Asterisks (**) denote the significant level P values=p<0.01. (***) Extremely significant p<0.001. The variations in the clinical and biochemical parameters Pre-induction and Post-induction were analyzed. All results are expressed as mean ±SEM and differences were considered significant.

Table 2: Vital signs, Serum biochemistry, hematologic parameters in mice. Comparison of Mean±SEM of pre and post anesthesia blood sample values in mice-Reference Control – Methohexital sodium

	Parameters	95%Confidence interval of Mean±SE the Difference			
		Pre-Induction Mean±SE	**Post-Induction Mean±SE**	**Lower**	**Upper**
REFERANCE CONTROL-GROUP -II	**VITAL SIGN:**				
	SBP(mmHg)	98.40±7.22**	116.40± 4.48	79.83	116.96
	DBP(mmHg)	62.56±3.60	68.36±4.83	53.3	71.81
	HR(bpm)	608.40±14.74*	643.10±10.28	570.5	646.3
	HEMATOLOGY:				
	RBC(x 10^{12}/l)	8.60±2.62**	8.2±2.1	3.83	8.36
	WBC (x 10^{9}	6.1±0.88*	7.63±0.46	6.18	13.01
	Hb(gm %)	9.6±1.33**	10.1±1.94	0.097	0.66
	PLATELETS (x 10^{9} /l)	312.22±13.87*	346.82±10.32	276.56	347.88
	BIOCHEMICAL:				
	ALT (IU/L)	36.22±2.47*	44.12±1.78	29.87	42.57
	AST (IU/L)	312.22±13.87*	346.82±10.32	276.56	347.88
	CREATININE(mg/dl)	0.6±0.03	0.9±0.18	0.52	0.67
	Na+(mM/L)	168.17±13.98**	153.28±10.34	132.33	204.11
	K+(mM/L)	7.2±1.38***	6.8±1.82	3.65	10.74
	Ca(mM/L)	4.3±1.77*	3.8±1.36	-0.25	8.85

The results of haematological and biochemical parameters recorded in group 2 animals at Statistical analysis of parametric data (Pre-induction and Post-induction compared) was performed using one-way analysis of variance (ANOVA) Asterisks (**) denote the significant level P values=p<0.01. (**) Extremely significant p<0.001,. (***),(*) P<0.05. The variations in the clinical and biochemical parameters Pre-induction and Post-induction were analyzed. All results are expressed as mean ±SEM and differences were considered significant.

Table 3: Hematologic measurements in propofol-anesthetized in mice Vital signs, Serum biochemistry, and parameter. Comparison of Mean±SEM of pre and post anesthesia blood sample values in mice-Test Dose – Propofol

	Parameters	95%Confidence interval of Mean±SE the Difference			
		Pre-Induction Mean±SE	**Post-Induction Mean±SE**	**Lower**	**Upper**
TEST DOSE (PROPOFOL)-GROUP -III	**VITAL SIGN:**				
	SBP(mmHg)	128.46±8.55	120.62±6.42	106.48	150.44
	DBP(mmHg)	76.32±3.33	71.41±2.26	67.75	84.88
	HR(bpm)	776.45±2.67	742.33±1.23**	769.59	783.21
	HEMATOLOGY:				
	RBC(x 10^{12}/l)	10.8±2.69	10.2±1.34	3.38	17.71
	WBC (x 10^{9}	14.4±1.14*	13.8±1.49	11.46	17.33
	Hb(gm %)	14.9±2.28*	13.2±1.88**	9.03	20.76
	PLATELETS (x 10^{9} /l)	623.32±14.22	610.18±10.84	586.76	659.88
	BIOCHEMICAL:				
	ALT (IU/L)	98.56±2.33	93.43±1.52	92.57	104.55
	AST (IU/L)	231.12±4.16*	229.53±3.68	220.42	241.82
	CREATININE(mg/dl)	1.91±0.33*	2.05±1.47	1.06	2.75
	Na+(mM/L)	172.31±10.86	162.31±08.24**	144.39	200.23
	K+(mM/L)	3.2±0.22	3.2±0.22		
	Ca(mM/L)	4.3±0.28*	3.8±0.16	3.58	5.02

The results of haematological and biochemical parameters recorded in group 3 animals at Statistical analysis of parametric data (Pre-induction and Post-induction compared) was performed using one-way analysis of variance (ANOVA) Asterisks (**) denote the significant level P values=p<0.01. (***) Extremely significant p<0.001, and (*) P<0.05. The variations in the clinical and biochemical parameters Pre-induction and Post-induction were analyzed. All results are expressed as mean ±SEM and differences were considered significant.

Table 4: Effect of potassium channel opener, Retigabine with propofol in mice, and values of vital signs, Serum biochemistry, Hematologic parameters in mice- Comparison of Mean±SEM of pre and post anesthesia blood sample values in mice of retigabine with propofol.

	Parameters			95%Confidence interval of Mean±SE the Difference	
		Pre-Induction Mean±SE	Post-Induction Mean±SE	Lower	Upper
Pretreated with Retigabine + Propofol-GROUP -IV	**VITAL SIGN:**				
	SBP(mmHg)	124.68±6.76	122.46±4.86	117.58	131.78
	DBP(mmHg)	77.46±2.46	74.72±2.92	74.87	80.04
	HR(bpm)	762.25±1.31	756.28±2.68	760.88	763.62
	HEMATOLOGY:				
	RBC(x 1012/l)	6.1±0.88*	6.8±1.62	5.17	7.02
	WBC (x 109	9.6±1.33*	10.0±2.47	8.2	10.99
	Hb(gm %)	5.38±0.11*	9.36±1..88	0.26	0.49
	PLATELETS (x 109 /l)	374.18±16.14**	380.87±10.12	357.24	391.12
	BIOCHEMICAL:				
	ALT (IU/L)	96.42±1.19	94.12±1.52	95.17	97.66
	AST (IU/L)	236.72±6.34	230.24±3.28	230.07	243.37
	CREATININE(mg/dl)	1.86±0.63*	1.5±1.48	1.19	2.52
	Na+(mM/L)	170.28±09.42**	165.82±08.46	160.39	180.17
	K+(mM/L)	7.3.±1.14*	6.9±1.28	6.1	8.49
	Ca(mM/L)	4.8±1.18*	4.0±0.86	3.56	6.03

The results of haematological and biochemical parameters recorded in group 4 animals at Statistical analysis of parametric data (Pre-induction and Post-induction compared) was performed using one-way analysis of variance (ANOVA) Asterisks (**) denote the significant level P values=p<0.01. (***) Extremely significant p<0.001, ,(*) denotes lower significance P<0.05. The variations in the clinical and biochemical parameters Pre-induction and Post-induction were analyzed. All results are expressed as mean ±SEM and differences were considered significant.

Table 5: Vital signs, Serum biochemistry, Hematologic parameters in mice. (n=6).Comparison of Mean±SEM of pretreated and post anesthesia blood sample values in mice- DAG lipase inhibitor RHC 80267 with retigabine.

	Parameters	Pre-Induction Mean±SE	Post-Induction Mean±SE	95%Confidence interval of Mean±SE the Difference	
				Lower	Upper
Pretreated with rhc 80267 with retigabine-GROUP -V	**VITAL SIGN:**				
	SBP(mmHg)	126.34±5.36	120.76±5.36	120.71	131.97
	DBP(mmHg)	76.82±1.96	73.58±1.34	74.76	78.87
	HR(bpm)	766.15±12.31	746.18±2.13	753.23	779.07
	HEMATOLOGY:				
	RBC(x 1012/l)	9.56±3.92*	8.60±2.62	5.44	13.67
	WBC (x 109	12.86±2.63*	10.32±1.22	10.1	15.62
	Hb(gm %)	14.2±2.37	14.1±1.26	11.71	16.68
	PLATELETS (x 109 /l)	13.9±2.32*	12.6±1.32	11.46	16.33
	BIOCHEMICAL:				
	ALT (IU/L)	74.26±13.20*	74.26±13.20	60.4	88.11
	AST (IU/L)	143.24±3.72***	156.37±2.52	139.84	147.14
	CREATININE(mg/dl)	0.7±0.53*	0.8±0.22	0.14	1.25
	Na+(mM/L)	142.22±1.65 **	148.12±1.36	140.49	143.95
	K+(mM/L)	5.9±2.33 *	6.2±1.12	3.45	8.34
	Ca(mM/L)	2.8±1.32*	3.2±0.38	1.41	4.18

The results of haematological and biochemical parameters recorded in group 5 animals at Statistical analysis of parametric data (Pre-induction and Post-induction) was performed using one-way analysis of variance (ANOVA) Asterisks (**) denote the significant level P values=p<0.01. (***) Extremely significant p<0.001,. , and (*) P<0.05. The variations in the clinical and biochemical parameters Pre-induction and Post-induction were analyzed. All results are expressed as mean ±SEM and differences were considered significant.

Table 6 : Comparison of Mean±SEM of pre and post anesthesia blood sample values in mice-Test Dose –RHC 80267 with Propofol. Hematologic measurements in propofol-anesthetized in mice Vital signs, Serum biochemistry, and parameter. (n=6).

	Parameters	Pre-Induction Mean±SE	Post-Induction Mean±SE	95%Confidence interval of Mean±SE the Difference	
				Lower	Upper
Pretreated with **propofol with rhc 80267 - GROUP -VI**	**VITAL SIGN:**				
	SBP(mmHg)	110.60±6.42*	106.40±5.22	94.09	127.11
	DBP(mmHg)	64.36±2.44*	62.56±2.60	58.08	70.63
	HR(bpm)	624.66±12.66*	618.68±10.64	592.11	657.21
	HEMATOLOGY:				
	RBC(x 1012/l)	6.8±1.28*	7.2±1.63	3.5	10.09
	WBC (x 10^9	10.2±2.68*	10.4±1..33	3.31	17.09
	Hb(gm %)	0.32±0.78*	0.38±0.34	-1.68	2.32
	PLATELETS (x 10^9 /l)	344.22±10.87	356.22±08.87	316.25	372.15
	BIOCHEMICAL:				
	ALT (IU/L)	38.76±2.66*	40.22±2.47	31.92	45.59
	AST (IU/L)	143.63±5.22*	148.23±3.56	130.21	157.05
	CREATININE(mg/dl)	0.7±0.62*	0.78±0.44	-0.89	2.29
	Na+(mM/L)	164.78±12.82	162.17±11.98	131.82	197.74
	K+(mM/L)	6.4±2.36	6.2±1.38	0.4	12.39
	Ca(mM/L)	3.8±2.24*	4.0±1.77	-1.95	9.55

The results of haematological and biochemical parameters recorded in group 6 animals at Statistical analysis of parametric data (Pre-induction and Post-induction compared) was performed using one-way analysis of variance (ANOVA) Asterisks (**) denote the significant level P values=p<0.01. (***) Extremely significant p<0.001 ,(*) denoted lesser significance i.e P<0.05. The variations in the clinical and biochemical parameters Pre-induction and Post-induction were analyzed. All results are expressed as mean ±SEM and differences were considered significant.

Table 7: Comparison of Mean±SEM of pre and post anesthesia blood sample values along with the level of significance (n=6). Vital signs, Serum biochemistry, Hematologic parameters in mice pretreated with Potassium channel blocker 4- Aminopyridine and Propofol.

		95%Confidence interval of Mean±SE the Difference			
Pretreated with4- Aminopyridine+ Propofo GROUP -VIII I	**Parameters**	**Pre-Induction Mean±SE**	**Post-Induction Mean±SE**	**Lower**	**Upper**
	VITAL SIGN:				
	SBP(mmHg)	124.68±6.76	122.82±5.46	117.58	131.78
	DBP(mmHg)	76.46±2.48	74.66±1.84	73.85	79.06
	HR(bpm)	768.88±2.46*	764.25±1.31	766.3	771.46
	HEMATOLOGY:				
	RBC(x 10^{12}/l)	10.4±2.69	10.2±1.78	7.57	15.55
	WBC (x 10^{9}	14.02±1.46	14.0±1.14	12.48	16.94
	Hb(gm %)	14.4±2.42*	14.0±1.28	11.86	632.45
	PLATELETS (x 10^{9} /l)	618.32±13.46	612.42±13.22	604.19	632.45
	BIOCHEMICAL:				
	ALT (IU/L)	38.32±1.67*	36.22±2.47	36.56	40.07
	AST (IU/L)	138.92±3.46*	132.43±4.58	135.29	142.55
	CREATININE(mg/dl)	0.7±0.18*	0.8±0.03	0.51	0.88
	Na+(mM/L)	172.38±10.42*	170.48±09.42	161.44	183.32
	K+(mM/L)	7.2±1.68**	7.0.±1.14	5.43	8.96
	Ca(mM/L)	4.4±1.38*	4.2±1.18	2.95	5.84

The results of haematological and biochemical parameters recorded in group 7 animals at Statistical analysis of parametric data (Pre-induction and Post-induction) was performed using one-way analysis of variance (ANOVA) Asterisks (**) denote the significant level P values=p<0.01. (***) Extremely significant p<0.001,. ,(*) P<0.05. The variations in the clinical and biochemical parameters Pre-induction and Post-induction were analyzed. All results are expressed as mean ±SEM and differences were considered significant.

Discussion

The purpose of a monitoring system in clinical medicine is not just to treat but to provide clinical information that may impact medical decision-making. Various techniques have been implemented in the pre-, intra-, and postoperative monitoring of surgical patients. Invasive and noninvasive methods facilitate the monitoring of nervous, cardiovascular,

respiratory, renal, and hematologic systems as well as of the metabolic status of the patients. While monitoring will not prevent all adverse incidents in the peri-operative period, it reduces the risks of accidents by permitting the continuous recording of core data such as heart rate, blood pressure, and peripheral oxygen saturation. Monitoring facilitates the detection of the consequences of human errors, while alerting physicians that a patient's condition is deteriorating for other reasons. On the other hand the mechanisms of activity of general anesthetics are still not completely unraveled. Previous studies suggest that Propofol can affect the levels of phospholipids and diacylglycerol and sphingosine in particular [37]. These in *vitro* data were consistent with the ability of halothane or propofol to stimulate PKC activity *in vivo* by increasing the sensitivity of PKC to endogenous phosphatidylserine, diacylglycerol and/or Ca^{2+}over their physiologic concentration ranges. Therefore this study probed the effects of the KCNQ potassium channels, and the effects of the Diacylglycerol lipase inhibitor RHC 80267 on the cardiovascular and hematological parameters [38].

We have found a marginal reduction in haemoglobin concentration following induction of anaesthesia with propofol as well as a decrease in red blood cells. Anaesthesia with propofol is known to reduce blood pressure and heart rate but in our study in the mice we noticed only a reasonable change as shown in Table 3. The reduction in RBC could be due to Splenic sequestration of blood elements could explain this result. The spleen as an organ is capable of sequestering the RBC's through splenic vascular relaxation. Many anaesthetic drugs can induce splenic vascular relaxation and causes a decrease in the circulating erythrocytes. Blood sequestration could also occur at different organs such as in skin, and skeletal muscles [39]

The prominent effect of Propofol anaesthesia is to cause hypotension. This hypotensive effect can reduce renal perfusion and result in the observed increase blood urea in this study [40]. The fact that there was no major concomitant increase in serum creatinine could be attributed to the fact that serum creatinine does not appreciably change until more the 30% of kidney function is lost. Based on these findings of this study, Propofol pretreated with KCNQ potassium channel opener retigabine between pre and post induction was found to affect hemodynamic and hematological, biochemical parameters. However the reference control methohexital treated alone, DAG lipase inhibitor with retigabine pretreated groups and there was not appreciable difference *in the* electrolyte level. In the cerebellum, DAGLα was predominantly expressed in Purkinje cells. DAGLα was detected on the dendritic surface and occasionally on the somatic surface, with a distal-to-proximal gradient from spiny branchlets towards somata. DAGLα was highly concentrated at the base of spine [41]. DAGLα is closely associated with postsynaptic spines and excitatory synapses are applicable to both neuron types [42]. In the group 4, DAG lipase inhibitor pretreated group with propofol there was less decrease found with hemodynamic and reversal of hematological parameters. In groups pretreated with Retigabine, RHC 80267 and Propofol showed decrease in DBP, heart rate and ALT. The modulation of biochemical parameters were compared with potassium channel blocker 4 Aminopyridine with propofol and this combination had little influence on the electrolytes like Na^+, K^+, and Ca^+ ions as well as hemodynamic parameters like the blood pressure (BP) and heart rate (HR). Although this is a study conducted in smaller rodents, it gives insight into the hemodynamics, hematological and biochemical parameters and more intensive research studies are required. Furthermore, it is important to know the basic levels of selected hemodynamic, biochemical, hematological and electrolyte indicators of blood while investigating the effects of various general anesthetic drugs in experimental animal models.

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