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Original Research Article

Hemostatic Parameters of Male Wistar Rats Treated with Ketamine and Different Kinds of Lignocaine

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Abstract: ***Background*****:** Anaesthesia is essential for successful surgical interventions to achieve complete immobilization, analgesia, muscle relaxation and unconsciousness. It facilitates pain-free surgical. Ketamine and lignocaine are examples of anaesthetic agents, often administered alone or in combination, for instance with anticholinergics or adrenaline, respectively. However, their effects on hemostatic and biochemical parameters are still subject of ongoing research. In this study, hemostatic parameters such as bleeding time, prothrombin time, activated partial thromboplastin time of male wistar rats treated with ketamine and different kinds of lignocaine were explored. ***Methodology*****:** 35 male wistar rats were used for the study. These animals were housed for one week for them to acclimatized before being sacrificed. Blood samples were collected using sample bottles and appropriate laboratory techniques were employed for laboratory investigations. Data obtained from this study was analysed using one way ANOVA. ***Discussion*****:** Ketamine and lidocaine when used both alone and in combination caused substantial variations in the haematological and biochemical parameters with the decrease in haemoglobin, level increase in erythropoietin and potassium, and an increase in plasma viscosity. Nevertheless, haemostatic parameters and erythrocyte integrity did not change, which means that there was low risk of coagulation. These implications present the possibility of renal and cardiovascular consequences that need a careful clinical application. ***Conclusion*****:** It is concluded that two different kinds of anaesthesia does not alter hemostatic cell lines and hence cannot cause hypercoagulation and hypocoagulation in users. Use of anaesthesia for surgical intervention is encouraged.

Keywords: Hemostatic Parameters, Ketamine, Lignocaine, Male Wistar Rats.

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1. INTRODUCTION

Anaesthesia such as ketamine and lignocaine/lidocaine play a very important role in modern medicine by ensuring surgeries without any pain. They achieve this by complete immobilization, analgesia, muscle relaxation and unconsciousness (Coasta, 2014).

Administration of lignocaine at high levels may have adverse reactions on hemostatic parameters. Post administration complications have been recorded in both lidocaine and ketamine anaesthesia which include erythropoietic collapse and hemolysis.

The major benefit of combining lidocaine and ketamine is to prevent central sensitization during surgical procedure ad intervention. Despite this benefit, it is reported by Tobiah *et al.,* (2018) that ketamine does not have significant impact on bleeding time, prothrombin time, and thrombin on volunteer human subjects.

In contrast to this, Roussi *et al.,* (2016) reported very high levels of fibrinogen, antithrombin III levels, platelet aggregation and bleeding time. Mazin *et al.,* (2018) reported that lignocaine concentration of 0.3% have prolonged initiation phase of clotting and low clotting stability. The report also depicted that 0.6% of lignocaine led to increase lysis and incubation of all phases of hemostasis.

These conflicting reports have necessitated the current study. Also, the little reports on hemostasis attributed to both ketamine anaesthetic agents and lignocaine is also a factor that necessitated this current study.

1.1. Aim of the Study

The aim of the study was to evaluate the impact of two different kinds of anaesthesia on hemostatic parameters of male wistar rats.

These hemostatic parameters include:

- Bleeding time
- Prothrombin time
- Thrombin time
- Partial thromboplastin time with kaolin
- Euglobinlysis time
- Platelet count

2. METHODOLOGY

2.1 Ethical Approval

This study was performed with animals treated in accordance with guide for the care and use of laboratory animals after securing ethical statement approval from the Research Ethics Committee (REC) of the Faculty of Basic Medical Sciences (FBMS), Rivers State University with REC approval number: RSU/FBMS/REC/23/160.

2.2. Experimental Animals

Thirty five (35) Wistar rats were acquired for the purpose of this study. The rats were housed in a well-ventilated room with adequate light source and temperature. The animals were fed adequately and allowed for acclimatization for one week before commencement of the experiment.

2.3. Drugs

The experimental rats were treated with 5mg/kg of ketamine according to Yohanne *et al.,* (2018) who used same doses of ketamine in his study while 2% of lignocaine at 2mg/kg according to Yakubu *et al.,* (2020) were administered to the experimental rats.

2.4. Experimental Design

Thirty five (35) male Wistar rats were divided into five (5) groups of six (6) rats each.

Group 1: This is the control group. The rats in this group were administered with 1ml of diluted distilled water orally for 2 days.

Group 2: Male Wistar rats in this group received 2mg/kg of plain lignocaine (lidocaine without adrenaline) for 2 days.

Group 3: Male Wistar rats in this group received 2mg/kg of lidocaine with adrenaline for 2 days.

Group 4: Male Wistar rats in this group received 5mg/kg of ketamine every day for 2 days.

Group 5: Male Wistar rata in this group received 5mg/kg of ketamine and 2mg/kg of lidocaine combined together everyday for 2days.

2.5. Collection of Blood samples from Experimental Rats

At the end of treatment with drugs, the rats were sacrified and blood samples collected by cardiac punctures into various sample bottles for haematological, hemostatic, haemorheological and biochemical investigations using appropriate techniques.

2.6. Estimation of Haemostatic Parameters

Bleeding time is measured by placing a blood pressure cuff on your upper arm and inflating it, tiny cuts made on the lower arm, cuff is removed when deflated and blotting paper placed on the cut every 30 seconds until bleeding stops. Bleeding usually lasts between 1-9 minutes bleeding time is measured from the time of incision to the moment bleeding stops, bleeding usually stop within 7-9 minutes.

Activated partial thromboplastin time is estimated by adding citrated plasma, an activating agent and phospholipid together and incubated at 30^0C. Calcium is added and the time necessary for clumping of kaolin is measured, the normal time is usually reported as less than 30-35 seconds.

Prothrombin time is estimated by adding citrated plasma and thromboplastin extract and incubating at 37^0c. The plasma is recalcified and the time

is measured until fibrin filaments are observed. The normal value is usually between 12-15 seconds.

Thrombin time is estimated by incubating citrated plasma at 37^0c and adding thrombin to the solution. Time is measured from the addition of the thrombin to the generation of fibrin filaments calcium is not necessary.

Fibrinogen level is measured by adding thrombin to plasma without calcium and the clot formed is washed and dissolved in a alkaline reagent than spectrophotometry is performed, absorbance at 282nm.

The clot is almost fibrin and the measured protein concentration is taken as equivalent to fibrinogen concentration.

2.7. Euglobin Clot Lysis Time/Fibrinolysis

Blood sample is collected into test tubes containing trisodium citrate as an anticoagulant and placed on ice. The sample is then centrifuged at 4^0c, the plasma sample is collected diluted with Asetic acid and incubated on ice for 15 minutes. A precipitate forms (The Euglobin Fraction of Plasma) which contains plasminogen, plasminogen activators and fibrinogen. The supernatant is collected by centrifugation at 4^0c, the supernatant is discarded and the precipitate is dissolved in buffer, this is then clotted with thrombin and the time to clot lysis determined by inspection every 15 minutes.

2.8. Estimation of Red Blood Cell Deformability

Diffraction ektacytometers and rheoscopes measured the mean deformability value for the total red blood cell population investigated and the deformation distribution index of individual cells respectively. Deformation assays of a whole single cell was possible by means of optical tweezers.

2.9. Estimation of Erythrocyte Aggregability

The rate and final extent of red blood cell aggregation was measured by means of rheoscopes (increase in light transmission during stasis).

2.10. Estimation of Erythrocyte Sedimentation Rate (ESR)

The westergren method was used which requires collecting 2ml of venous blood into a westergren tube containing 0.5ml of sodium citrate. It should not be stored not longer than 2hours at room temperature or 6 hours at 4^0c. The blood was drawn into a westergren-katz tube to 200mm mark, the tube is placed in a rack in a strictly vertical position for one (1) hour at room temperature, at which the time difference from the lowest point of the surface meniscus to the upper limit of the red cell sediment measured.

The distance of fall of erythrocytes expressed as millimetres in one (1) hour, is the ESR.

2.11: Statistical Analysis

Values for the results are pressed as meant SEM. The statistical analyses were done using the analysis of variance (ANOVA).

Computer softwares, Microsoft excel 2013 edition and SPSS 23.0 windows were used. Differences between mean were considered at $p<0.05$.

3. RESULTS

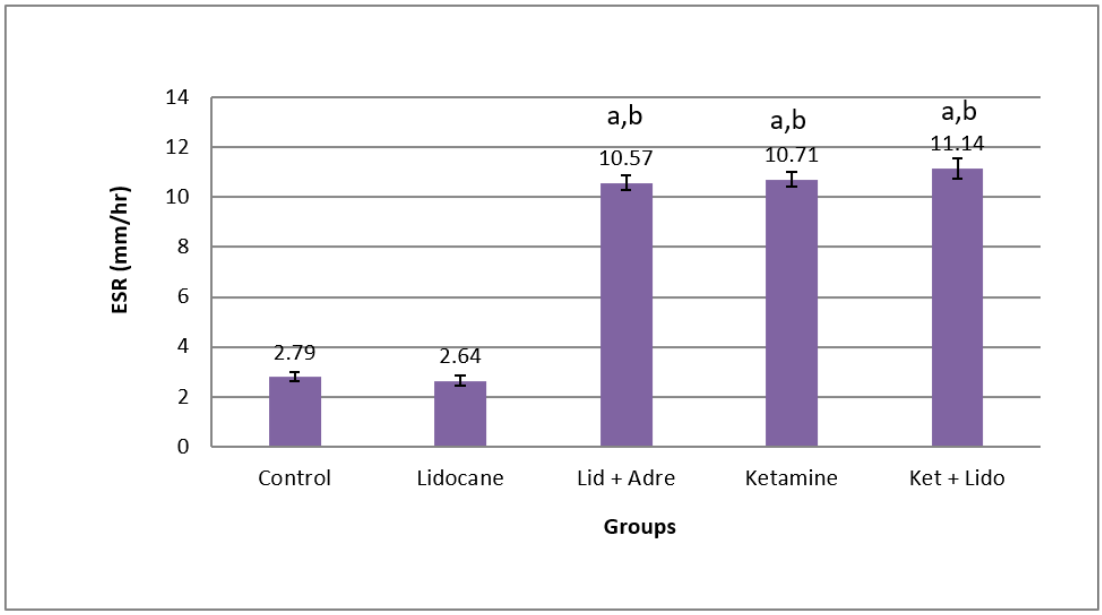

Figure 1: Comparing erytrocyte sedimentation rate in all the experimental groups. Results presented as mean ± SEM. a, b, c, and d = versus control, lidocane, Lid plus adre, and ketamine groups respectively at p<0.05

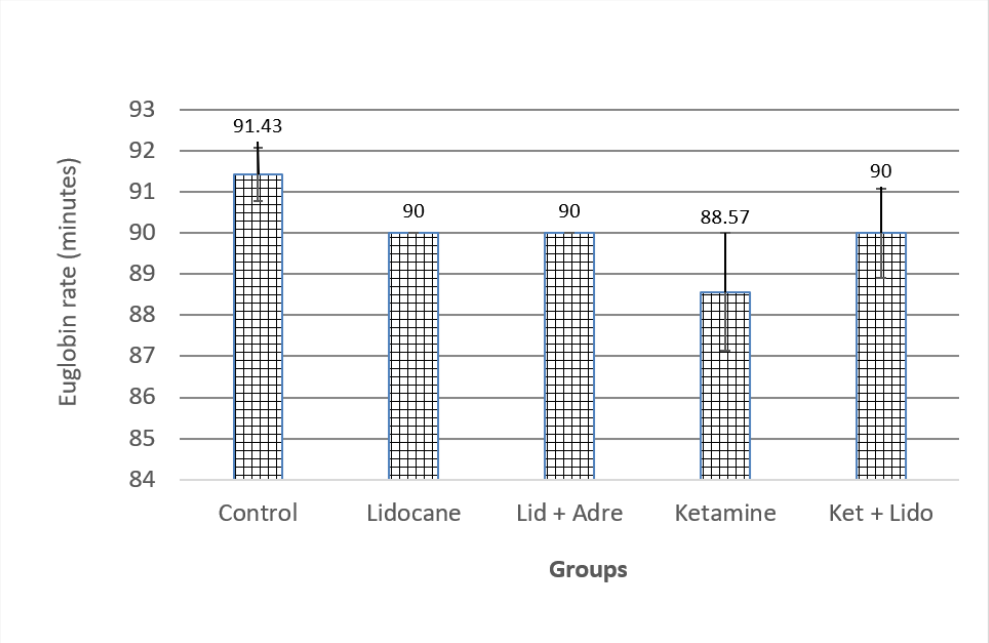

Figure 2: Comparing blood viscosity in all the experimental groups. Results presented as mean ± SEM

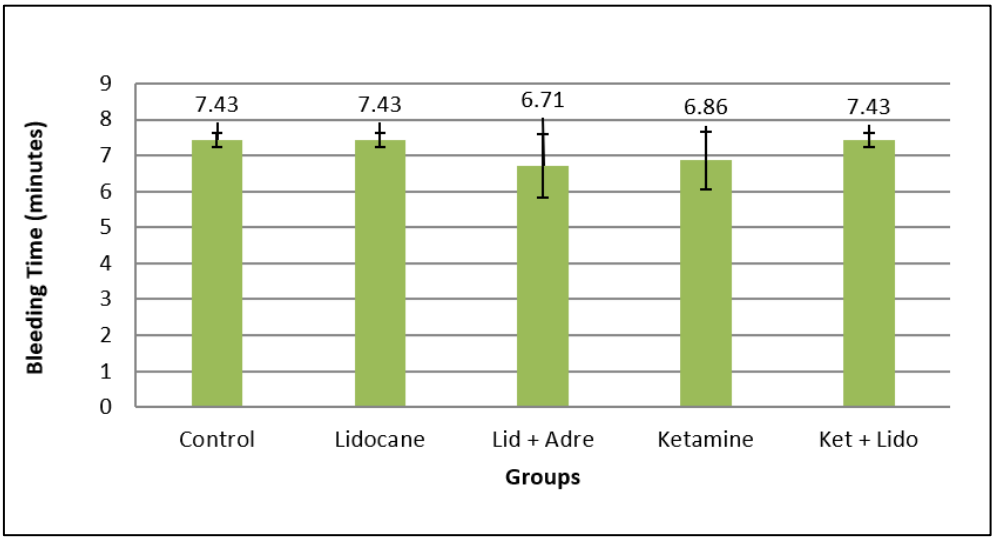

Figure 3: Comparing the bleeding time in all the experimental groups. Results presented as mean ± SEM

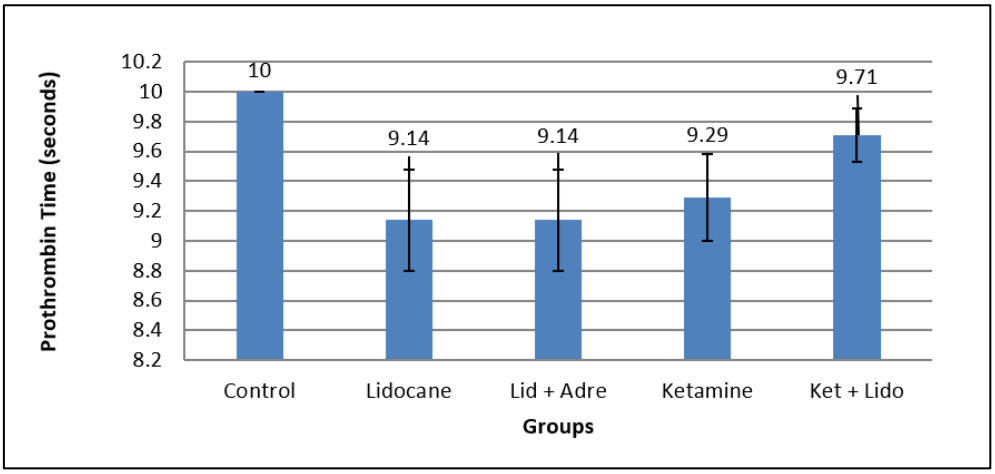

Figure 4: Comparing the prothrombin time in all the experimental groups. Results presented as mean ± SEM

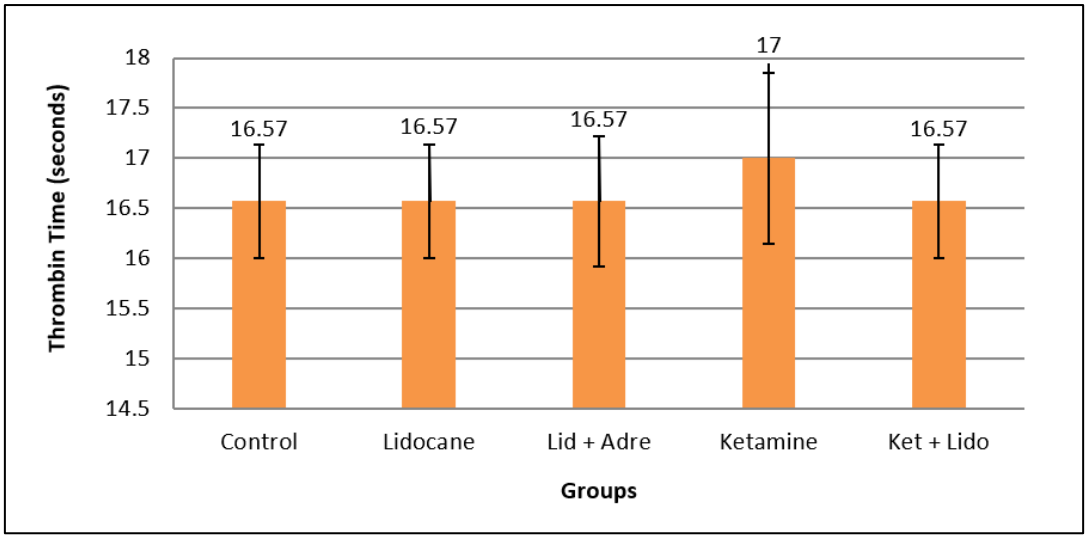

Figure 5: Comparing the thrombin time in all the experimental groups. Results presented as mean ± SEM

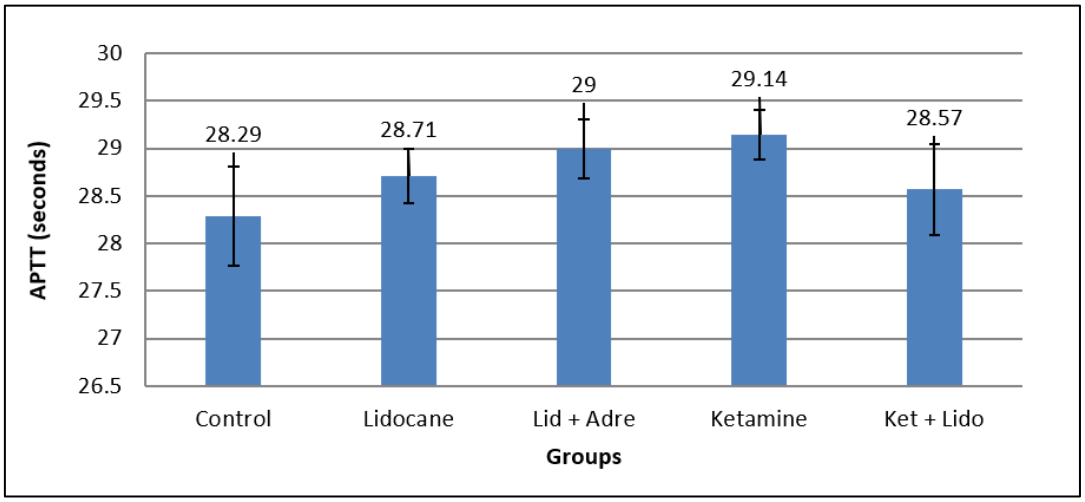

Figure 6: Comparing activated partial thromboplastin time in all the experimental groups. Results presented as mean ± SEM

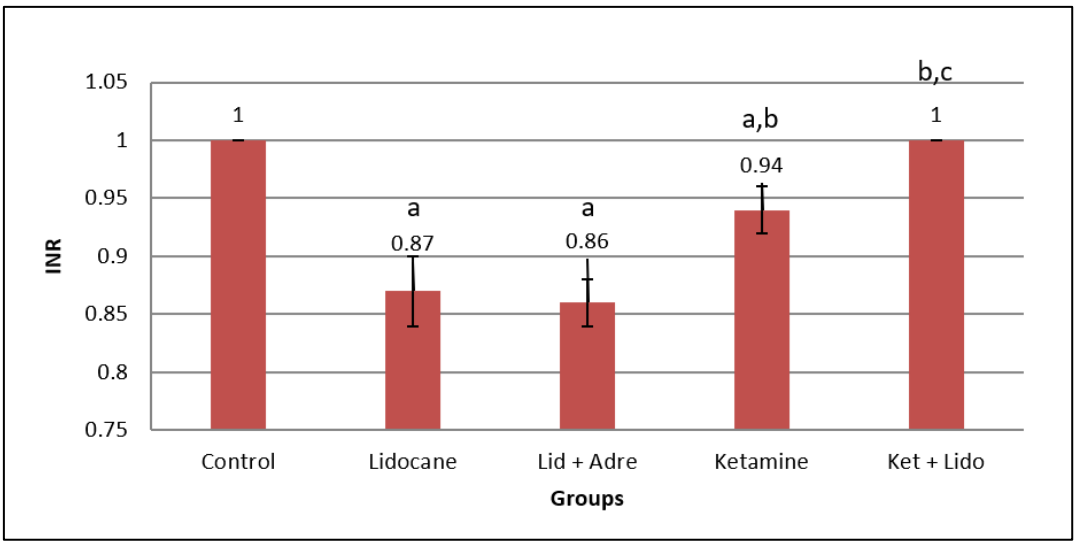

Figure 7: Comparing international normalises ratio in all the experiSmental groups. Results presented as mean ± SEM. a, b, and c = versus control, lidocane, and Lid plus adre groups respectively at p<0.05

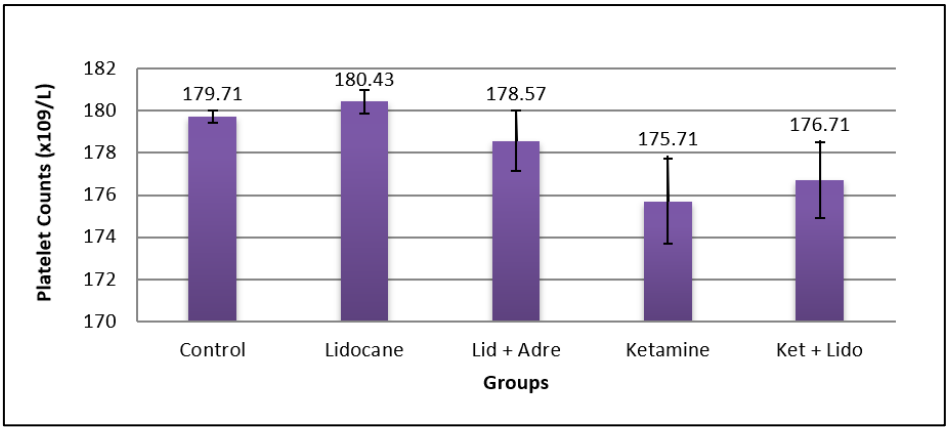

Figure 8: Comparing the platelet counts in all the experimental groups. Results presented as mean ± SEM

4. DISCUSSION

The results of this study showed a significant decrease in haemoglobin concentration with the combination of ketamine and lidocaine. This is consistent with the study of Gwebal *et al.,* (2012) who also recorded a reduction in haemoglobin concentration. However, the combination raised erythropoietin levels**.**

It was also observed that while anaesthetic agents did not cause any change in MCV value, MCHC was significantly raised. Haematocrit was unchanged, which, paired with lower haemoglobin, could contribute to greater oxygen delivery by erythrocytes. This study also showed that the anaesthetic agents did not alter erythrocyte membrane fragility; this indicates preserved red cell integrity and reduced anaemia risk. There was also an increase in the total white blood cell count and the neutrophils, lymphocytes and the monocytes in accordance with Amarpal *et al.,* (1998) but contrary to Sika (2013) who reported decrease in white blood cell count, neutrophils and lymphocytes in rats.

This research showed that anaesthetic agents showed no significant change in serum sodium and chloride ion concentrations. This report contradicts the reports of Clementina *et al.,* (2012) who reported increase in sodium with ketamine and lidocaine in goats; but supports the study by Destima *et al*., (2013) who reported a decrease in sodium with ketamine in human samples. The serum potassium level however rose to a very large extent, putting one at risk of developing hyperkalemia, especially when it is accompanied by potassium-increasing drugs. This causes renal and cardiovascular safety concerns in long-term ketamine use.

This study also showed that ketamine anaesthetic agent caused increased in blood urea nitrogen and creatinine levels and this is in consonance with the report of Clementina *et al.,* (2012) who reported increase in urea and creatinine with ketamine combined with lidocaine in goats. This may suggest possible renal impairment especially in patients with pre-existing kidney issues. There was also an increase in amounts of total protein, a decrease in globulin, and no changes in albumin or fibrinogen. And although viscosity in the blood did not change, the viscosity of plasma did, and this may raise cardiovascular risk.

Additionally, this study observed that both ketamine and lignocaine does not significantly alter hemostatic parameters, such as bleeding time, thrombin time, prothrombin time, partial thromboplastin time with kaolin as well as euglobinlysis time. This finding is comparable and consistent with previous reports of Tobiah *et al* (2018) who depicted that ketamine does not have significant effect on bleeding time, prothrombin time and thrombin time of human volunteer subjects.

This current study contradicts the reports of Mazin *et al.,* (2018) who reported increase in lysis of hemostatic cell lines and inhibition of all phases of hemostasis.

5. CONCLUSION

The following conclusions are drawn from the current study:

1. That two different kinds of anaesthesia does not alter hemostatic cell lines
2. That both ketamine and lignocaine does not have the tendency of cause euglobinlysis.
3. That both ketamine and lignocaine does not cause hypercoagulation and hypocoagulation.

6. RECOMMENDATION

The following recommendations are drawn from the study:

1. Use of anaesthesia for surgical procedure is encouraged.
2. Use of both ketamine and lignocaine for surgical interventions are beneficial since it does not alter hemostatic cell lines.
3. Both ketamine and lignocaine anaesthetic agents does not cause hypercoagulation as well as hypocoagulation.

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