Effect of low-dose ketamine pretreatment to etomidate on serum cortisol levels in critically ill cardiac patients: A Randomized clinical trial

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Research Article

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Abstract

Background: This study aimed to evaluate the effect of low-dose ketamine pretreatment to etomidate on serum cortisol levels in critically ill cardiac patients with acute anemia undergoing upper endoscopy and Colonoscopy

Patients and Methods: Sixty adult cardiac patients, ≥ 18 years, who underwent upper endoscopy and Colonoscopy to manage acute anemia in the cardiac intensive care units were enrolled. Patients were randomly divided into two groups: **Group (E):** received etomidate 0.2 mg/kg IV followed by etomidate 0.05 mg/kg IV, and **Group (KE):** received ketamine 0.5 mg/kg IV, then etomidate 0.1 mg/kg IV, followed by etomidate 0.05 mg/kg IV. The primary outcome was Serum cortisol level at 6 hours after the procedure. The secondary outcomes: Estimated change in serum cortisol level (6-hours postoperative value compared to preoperative one), the incidence of any adverse effects, patient satisfaction, and total etomidate dose.

Results: The mean postoperative cortisol level significantly reduced in group E than group KE; (295.60±49.218) mcg/dL versus (461.00 ±67.946) mcg/dL respectively With 95% CI = 351.94 to 404.66. In addition, the estimated serum cortisol reduction level was also significant between groups; In group E, the estimated cortisol level decreased nearly 53% from 632.40±35.066 mcg/dL to 295.60±49.218 mcg/dL six hours postoperative. While in group KE, the estimated cortisol level decreased only 27% from 639.13±43.035 mcg/dL to 461.00±67.946 mcg/dL.

Conclusions: low-dose ketamine pretreatment to etomidate can successfully control etomidate-induced adrenocortical suppression and minimize the decrease in serum cortisol level in critically ill cardiac patients with no additional adverse effects.

Trial Registration:

This study is registered on ClinicalTrials.gov (NCT04857450; principal investigator: Mostafa Mohammed Elsaid Elhamamsy; registration date: 23/04/ 2021).

Introduction

Gastrointestinal (GI) bleeding is frequently seen in critically ill cardiac patients in ICU due to many causes, including the toxicity of anticoagulation therapy, stress ulceration, chronic peptic ulcers, or neoplasms. [(1)] It has been stated that, after three days in the ICU, 95% of patients had hemoglobin drop. Therefore, upper GI bleeding should always be diagnosed by Esophagogastroduodenoscopy (EGD) [(2)], while lower GI bleeding should always be diagnosed by Colonoscopy. However, both are lengthy and painful procedures. SO, general anesthesia with hemodynamic stability is needed to achieve this target in critically ill cardiac patients. [(3)]

Etomidate possesses unique, desirable properties such as rapid onset and short duration of action. In addition, it produces less apnea than barbiturates or propofol, no histamine release, infrequent allergic reactions, relative cardiovascular and respiratory stability, and neuroprotective effects, making it an attractive induction agent to facilitate this procedure. [4, 5] However, etomidate side effects also exist, including pain on injection, myoclonic movements during induction of general anesthesia, and postoperative nausea and vomiting (PONV). [6] Furthermore, one of the most dangerous etomidate toxicity among anesthetic drugs is the dose-dependent inhibition of adrenal steroid synthesis that far outlasts its hypnotic action, and that may reduce survival of critically ill patients. [7] It has been shown that in patients undergoing elective surgery, cortisol response to surgery was absent 48 hours after administering a single bolus of etomidate. [8]

Ketamine is a potent, multimodal dissociative anesthetic. It is one of the well-known MNDA antagonists. [9] Several years ago, NMDA receptors were involved in the physiologic regulation of hormones released from the hypothalamic-pituitary-adrenal axis. [9] Several clinical trials have demonstrated that ketamine is associated with increased postoperative serum cortisol levels. [10] Low-dose ketamine pretreatment was successfully used to reduce the incidence and severity of etomidate-induced myoclonus. [11] However, no available data about its role in controlling etomidate-induced adrenal suppression. So, we aimed to evaluate the efficacy of low-dose ketamine pretreatment to etomidate on serum cortisol levels in anesthesia for critically ill cardiac patients.

We hypothesized that Low dose ketamine (0.5 mg/kg) pretreatment to etomidate could be helpful to minimize the decrease in serum cortisol level after etomidate administration and decrease the total dose of etomidate used in such critically ill patients. The primary outcome was Serum cortisol level 6 hours after the procedure.

Patient And Methods

This prospective, randomized, triple-blind clinical trial was performed following the tenets of the Declaration of Helsinki. Institution review board (IRB), King Saud University, Saudi Arabia approval was obtained (Ref. No. 21/0047/IRB), and written informed consent was acquired from all patients. the study protocol was registered at ClinicalTrials.gov. (NCT04857450; principal investigator: Mostafa Mohammed Elsaid Elhamamsy; date of registration: April 23/04/ 2021). This study adheres to the applicable CONSORT guidelines.

The study included sixty cardiac patients admitted to the ICU at King Saud University and scheduled for EGD and Colonoscopy to diagnose and manage acute anemia aged 18 – 65 years, ASA III-IV, with ejection fraction (EF) > 30% were included. The Exclusion criteria were as follow: poor left ventricular function (ejection fraction < 30%), recent myocardial infarction (last seven days), known allergy to midazolam, fentanyl, etomidate, or ketamine, severe respiratory, hepatic, and renal failure, or history of neurological disorders or convulsions.

The study was performed in the ICU with the presence of all emergency equipment. Patients were randomly divided into two groups (E; etomidate and KE; ketamine/etomidate groups) using computer-generated random numbers placed into separate opaque envelopes opened by the study investigator just before performing the procedure. The gastroenterologist who performed the colonoscopies, all participants, and data collectors were blinded with group allocation till the end of the study. All patients received a standard colonic preparation protocol and were fasted eight hours before the procedures.

Anesthesia management:

Standard monitoring was performed after establishing IV access (noninvasive blood pressure, ECG, SpO2, and Bispectral Index (BIS)). First, a nasal cannula for oxygen (6 l/min) was connected to all patients. Then midazolam 0.03mg/kg IV and fentanyl one µg/kg IV were injected in all patients as a premedication.

For Group (E)

Patient Received etomidate 0.2 mg/kg IV over 30 seconds, followed by 0.05 mg/kg IV and repeated when needed.

For Group (KE)

Patient Received ketamine 0.5 mg/kg IV over 30 seconds, then etomidate 0.1 mg/kg IV over 30 seconds, followed by 0.05 mg/kg IV and repeated when needed.

The anesthesiologist determined the additional dose of etomidate to achieve a BIS above 60.

Any adverse effect was recorded, including; **1- Hypotension**: decrease of baseline systolic blood pressure (SBP) >30%, or decrease of baseline diastolic blood pressure (DBP) >30%, this was treated by phenylephrine 100-200 µg IV boluses. **2- Bradycardia**: decrease of HR < 50/min; atropine 0.5 mg IV boluses managed this. **3- Apnea**: spontaneous breathing > 30 sec, or SpO2 < 85% and this was treated by assisted manual ventilation using an AMBU bag and face mask.

At the end of the procedure, the total etomidate dose, the duration of the procedure, and the recovery time of the patients were recorded.

After full recovery and when the patients were alert enough to express their attitude regarding the intra-procedural events, they were asked to score their level of satisfaction during the procedure to recall any painful or other undesirable intra-procedural events.

Patient's satisfaction level was assessed with a Likert five-item scoring system [12]: (1 = Not satisfied at all, 2 = slightly satisfied, 3 = somewhat satisfied, 4 = very satisfied, and 5 = extremely satisfied). Finally, serum cortisol levels both before and 6 hours after the procedure were measured to calculate the percentage of suppression in both groups.

The primary outcome was; 6 hours postoperative serum cortisol level.

Secondary outcomes included

Estimated change in serum cortisol level (6-hours postoperative value compared to preoperative one), Incidence of perioperative complications; hypotension, bradycardia, apnea, nausea/vomiting, and psychological reactions. Patient satisfaction and Total dose of etomidate.

Statistical Analysis

For sample size calculation, there were no previous studies at the time of designing the study protocol, so we performed an external pilot study that included seven patients in each group, with its results not included in the full-scale study. This pilot showed 6 hours postoperative serum cortisol level (mean±SD, 356.28± 39.343 in the E group versus 389.71± 45.76 in the KE group). The minimal sample size of patients was 27 in each group needed to get power level 0.80 and alpha level 0.05. the calculated sample size was increased by 10% to reach 30 in each group to overcome the data dropout.

The collected data were organized, tabulated, and statistically analyzed using SPSS software statistical computer version 22 (SPSS Inc, USA).

We used a two-sample t-test to compare the two groups' mean values (age, weight, EF, Procedure Time, Recovery Time, and Serum cortisol level) and data presented as Mean, standard deviation (SD). And The Chi-square test was used to analyze independent qualitative data. Fischer's test was used when chi-square test conditions were not met. Data were presented as numbers and percentages (Sex, ASA, and the Side effects), and (95% CI) were estimated. A two-sided P-value of <0.05 was considered statistically significant.

Results

For this study, 68 patients were assessed for eligibility based on the inclusion and exclusion criteria. Eight patients have excluded; three cases with EF below 30 %, four patients declined to participate, and one patient developed severe intraoperative bleeding from esophageal varices and was intubated to avoid aspiration. The remaining 60 patients were randomly assigned into the study groups **(**Figure 1**).**

The demographic characteristics and operative data concerning age, sex, body weight, ASA physical status, the length of the procedure, and the time needed for recovery were similar between the two groups **(**Table 1**)**.

Table 1
Demographic Characteristics and Operative Data

	Group E	Group KE
Sample size ,n	30	30
Mean age (SD) in (years)	49 (11.59)	50.07 (11.20)
Mean Weight (SD) in kg	78.70 (8.774)	81.13 (8.905)
Sex, n (%)		
Male	17 (56.66)	16 (53.33)
Female	13 (43.33)	14 (46.66)
ASA, n (%)		
III	27 (90)	26 (86.66)
IV	3 (10)	4 (13.33)
Mean Procedure Time (SD) in minutes	28.80) 4.686(	28.97) 4.476(
Mean Recovery Time (SD) in minutes	11.83) 2.335(	12.53) 2.36(

The mean six hours postoperative serum cortisol level significantly reduced in group E than group KE; (295.60±49.218) mcg/dL versus (461.00±67.946) mcg/dL respectively With 95%CI = 351.94 to 404.66; p=0.000 (Table 2). In addition, the estimated serum cortisol reduction level was also significant between both groups; In group E, the estimated cortisol level decreased nearly 53% from 632.40±35.066 mcg/dL before the procedure to 295.60±49.218 mcg/dL six hours after the procedure. While, in group KE, the estimated cortisol level decreased only 27% from 639.13±43.035 mcg/dL before the procedure to 461.00±67.946 mcg/dL six hours after the procedure ($p < 0.05$) (Figure 2).

Table 2
Serum cortisol level pre-and 6 hours postoperative

	Group E	Group KE	95%CI	P-value [a ,b]
Sample size, n	30	30		
Mean Preoperative cortisol (SD) in (mcg/dL)	632.40 (35.066)	639.13 (43.035)	625.67 to 645.86	0.728
Mean 6 hours Postoperative cortisol (SD) in (mcg/dL)	295.60 (49.218)	461.00 (67.946)	351.94 to 404.66	0.000

The total dose of etomidate was significantly different between the two groups being 34.10±5.095 mg in group E versus 23.93±4.346 mg in Group KE (P<0.001) (Figure 3).

There was no significant difference between the groups regarding patient satisfaction (Table 3). In addition, there was no significant difference between the groups regarding the incidence of adverse effects during the procedure.

Table 3
Patient satisfaction:

	Group E	Group KE	95% CI	P-value [a ,b]
Sample size ,n	30	30		
Patient Satisfaction, n (%)	3(10%)	5(16.66%)	4.09 to 4.44	0.520
Slightly Satisfied	13(43.33%)	15(50%)		
Very Satisfied	14(46.66%)	10(33.33%)		
Extremely Satisfied				

Discussion

Our study shows that serum cortisol levels were reduced in both groups at 6 hours postoperatively compared to preoperative levels. However, there was a marked reduction in the etomidate group (E) than the ketamine/etomidate (KE) group, which was statistically significant (p = 000). These findings meet that A. K. PANDEY et al. [10] reported that serum cortisol levels decrease significantly after etomidate administration while increasing significantly after ketamine administration.

Etomidate is well known to decrease serum cortisol levels. Several reports in the literature have described adrenocortical suppression after single-dose administration of etomidate with reversibility in normal healthy subjects. [13–15] On the other hand, N. Hergovich et al. [16] reported a significant increase in serum cortisol after ketamine administration in healthy volunteers. Furthermore, ketamine infusion has been described as a dose-dependent increase in serum cortisol level in an animal study. [17]

Etomidate-induced adrenocortical suppression could hinder survival in critically ill patients [11]. On the other hand, increased serum cortisol after ketamine administration worsens surgical-induced stress response. [10] So, we successfully used minimal-dose ketamine as a pretreatment to etomidate to counteract its effect on serum cortisol. Low-dose ketamine pretreatment to etomidate was used safely and successfully to reduce etomidate-induced myoclonus [11]. But, to our knowledge, no available studies about the role of ketamine in controlling etomidate-induced adrenocortical suppression.

The mechanism of anesthetic effects on the adrenocortical function and steroidogenesis remains unclear. However, etomidate-induced adrenocortical suppression has been explained by directly inhibiting the enzymes involved in cortisol biosynthesis, especially the final enzyme in the cascade, 11 β-hydroxylase. [18] In their animal study, Besnier E et al. [18] described an effect of ketamine on the

hypothalamic-pituitary-adrenal axis (HPA) similar to that of etomidate. However, no clinical evidence supports these findings.

Also, we found no significant difference between both groups regarding hemodynamics, side effects, recovery time, recalling, or patient satisfaction, with favorable outcomes. These findings support the hypothesis elicited by the authors that low-dose ketamine pretreatment to etomidate can successfully counteract the effect of etomidate on serum cortisol without additional side effects or aggravation of stress response. This is met with Wu GN et al. [11] as they found that ketamine reduced the incidence and severity of myoclonus without any additional adverse effects.

Based on the current study's findings described by Wu GN et al. [11], low-dose ketamine pretreatment to etomidate could be used safely and has favorable outcomes than etomidate alone. This elicits a question about adding ketamine to etomidate to make a new preparation (Ketamine-etomidate) that can achieve the benefits of both drugs without any additional adverse effects.

Limitations

an important limitation of our study is the short time follow-up (only 6 hours) so, we could not test the reversibility of serum cortisol to baseline values after anesthesia. Also, our study population was specific with unique characteristics; all are critically ill cardiac patients with acute anemia, which could limit our data's generalizability. In addition, lack of available data for comparison as this is the first clinical trial testing the effect of low-dose ketamine pretreatment to etomidate on postoperative cortisol levels. Despite these limitations, our study highlights the successful role of ketamine pretreatment in minimizing the decrease in serum cortisol level after etomidate administration.

Conclusion

low-dose ketamine pretreatment to etomidate can successfully control etomidate induced adrenocortical suppression and minimize the decrease in serum cortisol level in critically ill cardiac patients with acute anemia undergoing upper endoscopy and Colonoscopy with no additional adverse effects.

Abbreviations

GI: Gastrointestinal

EGD : Esophagogastroduodenoscopy

Declarations

Ethics approval and consent to participate:

Institution review board (IRB) King Saud University, Saudi Arabia, Permission was obtained (Ref. No. 21/0047/IRB). Written informed consent was attained from all patients. All methods were performed

following the relevant guidelines and regulations.

Consent for publication:

Written informed consent was attained from all patients

Availability of data and materials:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare no conflicts of interest.

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Authors' contributions

Data collection: MAH,MAH,FBZ,AMA

Data analysis: MAH,S,MAH, SAA

Writing: MAH,MAA,MMH,MLB,GFM

Revising: MAH,MLB,MAH,MMH,SAA

Study design: MAH,MLB,MMH,MAH

Patient recruitment: MMH

All authors contributed equally to this work.

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Figures

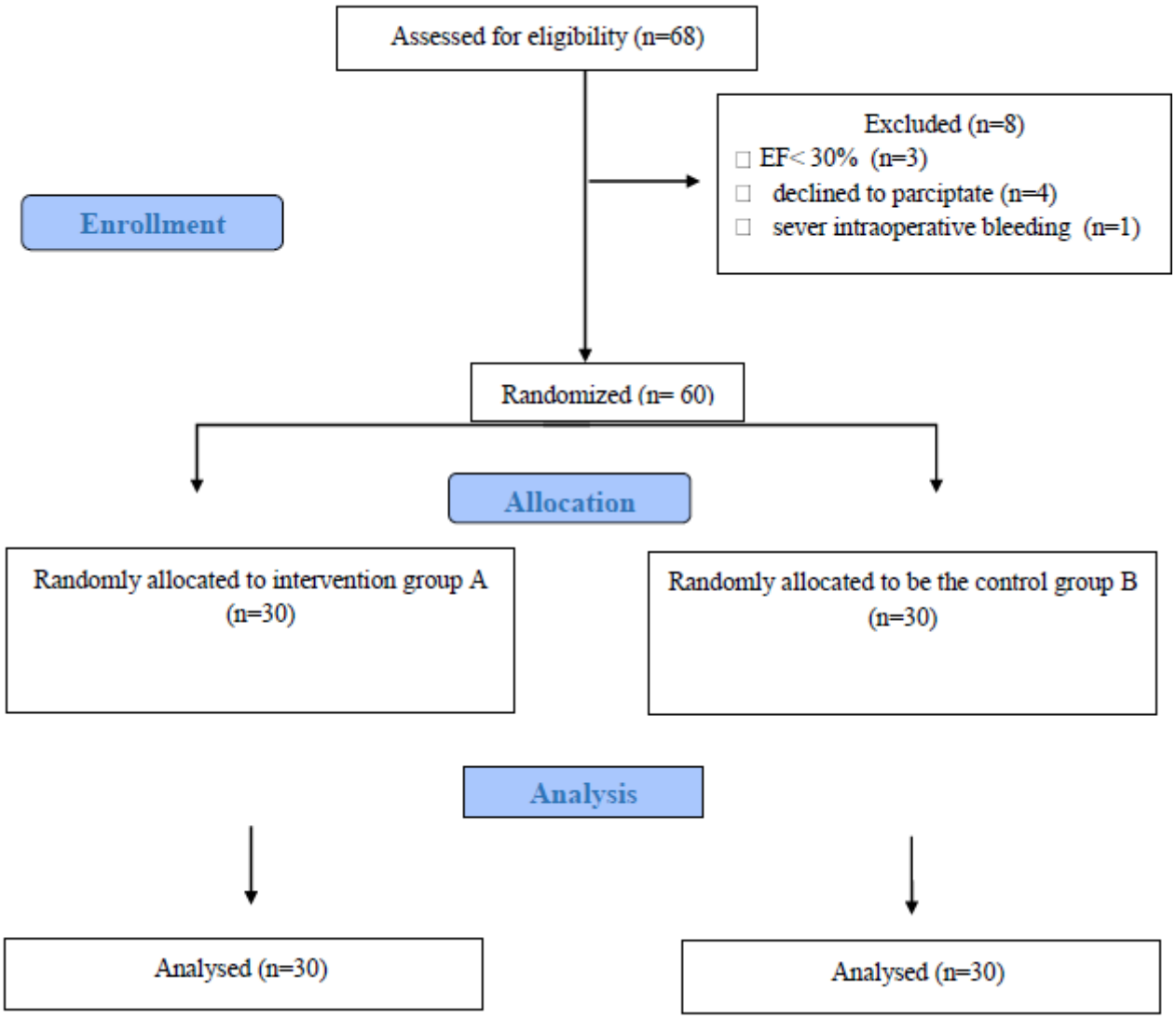
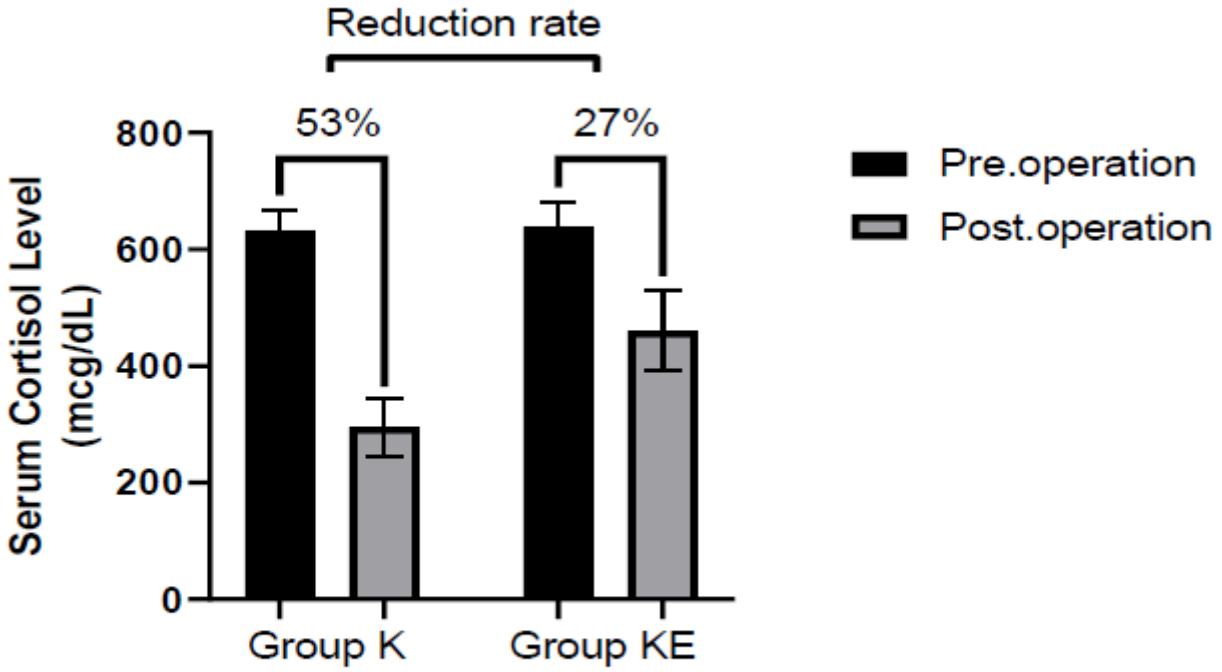


Figure 1

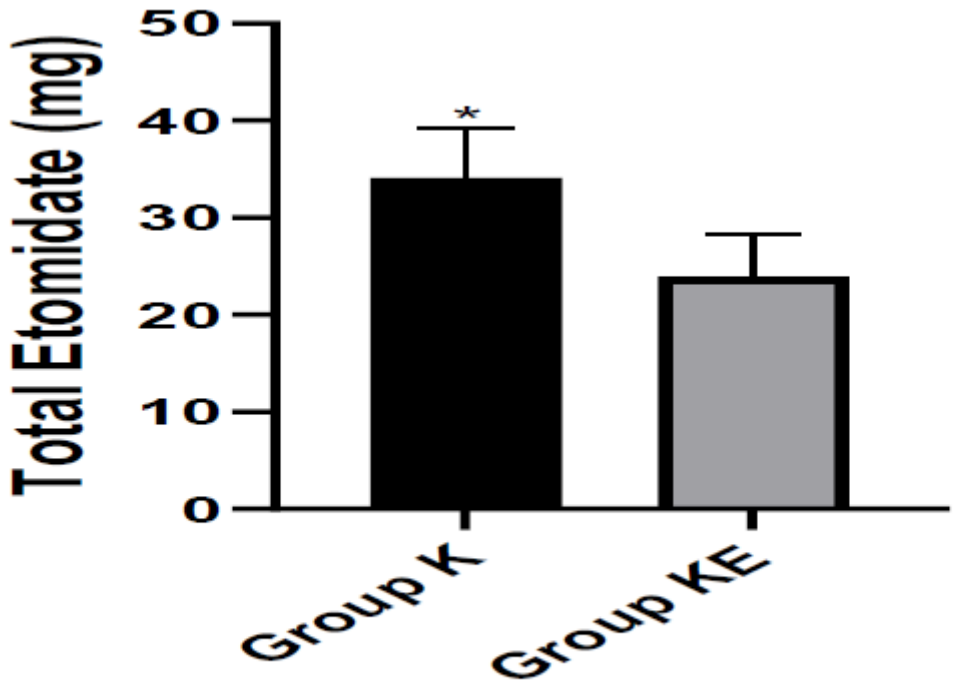
Consort flow diagram of the study population.



Abbreviations: Group K, Etomidate group; Group KE, Ketamine Etomidate group.

Figure 2

Serum cortisol level pre-and 6 hours postoperative.



Abbreviations: Group K= Etomidate group, Group KE= Ketamine Etomidate group.

Figure 3

The total dose of etomidate.