ORIGINAL ARTICLE

# Suppression of Cortisol Levels by a Bolus Dose of Etomidate in Patients Undergoing Laparoscopic Cholecystectomy

S Charuvi[1], Hiremathada Sahajananda[2], S Dwajani[3]


## Abstract

**Aim and objective:** The main purpose of the study was to determine the effect of a bolus dose of etomidate on serum cortisol levels in patients undergoing laparoscopic cholecystectomy. As there are a lot of controversies regarding this, detailed research was carried out to find answers regarding the question as to whether etomidate suppresses the cortisol levels or not.

**Materials and methods:** In this prospective interventional study, 31 ASA physical status I and II patients undergoing laparoscopic cholecystectomy were enrolled. Pre-anesthetic medication consisted of the tab. diazepam 5 mg the previous night and tab. ranitidine 150 mg the previous night and the next day morning at 5 am with sips of water. The patient was then induced with 0.4 mg/kg of etomidate intravenously. Skeletal muscle relaxant vancuronium of 0.1 mg/kg was administered. Intubation was performed with an appropriate endotracheal tube. Anesthesia was maintained with $N_2O$, $O_2$, and isoflurane. After surgery, the patient was reversed using neostigmine and glycopyrrolate. The patient was extubated when awake and then shifted to the recovery room and after one hour to the postoperative ward. Three venous samples, 2 mL each were drawn from each patient. The first blood sample T1 was drawn at 9 am on the day of the surgery before the induction of etomidate, the second blood sample T2 was 1 hour after the induction of etomidate which coincided with pneumoperitoneum, and the third blood sample T3 was drawn at 9 am the following morning. After the blood samples were collected in the red top vacutainers, they were allowed to clot naturally for about 30 minutes at room temperature after which tubes were centrifuged for 15 minutes at 1,000, 2,000, and 3,000 rpm, respectively, for the first, second, and third samples. After the separation of the serum, they were stored at −80°C until analysis. Sample analysis for cortisol estimation was done using Cobas E-411 machine using the electrochemiluminescence method. The statistical analysis was applied to analyze the demographic data, Chi-square test for categorical variables. Analysis was done using RM-ANOVA and significance was set at $p < 0.05$.

**Results:** The statistical analysis showed the above table shows that males showed mean cortisol values of 11.48 ± 2.05 at time T1 which was at baseline, 9.78 ± 1.72 at time T2 which was at pneumoperitoneum, and 5.038 ± 4.22 at time T3 which was at 24 hours. The female patients showed mean cortisol values of 13.407 ± 2.33 at T1, 11.47 ± 2.65 at T2, and 7.065 ± 5.41 at T3. The combined mean cortisol levels of the patients were: 12.291 ± 1.57, 10.49 ± 1.52, and 6.085 ± 3.36 at intervals of T1, T2, and T3, respectively. According to the Student's *t*-test, the cortisol levels show that the *p* value (0.11) between T1 vs T2 does not show any significance. The *p* value (0.001) of T1 vs T3 is extremely significant and shows cortisol suppression and helps in proving the objective of the study. The *p* value (0.02) of T2 vs T3 was significant and shows that the cortisol levels are suppressed.

**Conclusion:** Hence, this study showed that the cortisol levels are suppressed by a bolus dose of etomidate in patients undergoing laparoscopic cholecystectomy. It was not related to any adverse outcome. The major advantage of etomidate over other available intravenous induction agents is attributed to the remarkable cardiovascular stability it offers in patients with cardiac disease. It provides a "stress-free" state, in children which is of importance in high-stress surgeries like the Intracardiac repair of Tetralogy of Fallot using Cardiopulmonary Bypass. Its use probably could be restricted to those situations where it offers a clinical advantage over other available drugs until the clinical relevance of the adrenal suppression effects of etomidate is fully known.


**Keywords:** Cortisol levels, Etomidate, Laparoscopic cholecystectomy.

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## Introduction

Cortisol, a steroid hormone belonging to the glucocorticoid class of hormones, is released during the "fight or flight" reaction. This stress hormone is produced by the adrenal gland and its release is controlled by the hypothalamus part of the brain. The hormone has its peak levels early in the morning and reaches its lowest levels at about midnight. The release of ACTH from the pituitary gland in response to stress is the principal stimulus to cortisol production by the adrenal cortex and also increases aldosterone production. An altered pattern of serum cortisol levels has been observed during trauma, surgery, fear, and pain. Cortisol levels may reach from 400 to 1500 nmol/L in 4–6 hours depending on the severity of surgical trauma.[1]

Certain general anesthetics like etomidate are known to suppress cortisol levels in patients undergoing surgery. Many authors suggest that this inhibition is reversible in normal healthy

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subjects.[2] Etomidate is a short-acting agent that has rapid onset and recovery, good/safe cardiovascular profile and so is a good induction agent for patients with poor cardiac functions. Etomidate is given as a bolus I.V dose of 0.4 mg/kg and has a half-life of about 75 minutes. It has a rapid onset of action of 30–60 seconds and a duration of action of 3–5 minutes. It is known to cause primary adrenal suppression in the adrenal cortex by reversibly inhibiting 11-beta hydroxylase, an enzyme important in adrenal steroid production.[3]

Etomidate is used for conditions like rapid sequence induction and intubation, dilatation and curettage, lowering intracranial pressure, hypovolemia, and also in patients undergoing cardiac surgery, laparoscopic cholecystectomy.

Laparoscopic cholecystectomy is a minimally invasive surgery that describes the performance of surgical procedures with the assistance of a laparoscope after creating a pneumoperitoneum. Pneumoperitoneum produced during laparoscopy also results in progressive and significant increases in plasma concentrations of cortisol, epinephrine, norepinephrine, and renin.[4]

Important questions relating to the effect of etomidate on adrenocortical reserve after a short intraoperative infusion or a single induction dose remain unanswered.[5]

Among general anesthesia induction drugs, etomidate is the only imidazole, and it has the most favorable therapeutic index for single bolus administration. It also produces unique toxicity among anesthetic drugs—inhibition of adrenal steroid synthesis. Preclinical experiments in mammals also demonstrated that etomidate injection was associated with minimal hemodynamic changes or respiratory depression, features that were presumed to result in its unusually favorable safety profile. It blocks the synthesis of both aldosterone and cortisol. A single induction dose of the drug will suppress hormone production for 6–12 hours while infusion for 1–2 hours blocks cortisol synthesis for up to 24 hours.[1]

Due to its lack of effect on the sympathetic nervous system and on baroreceptor function,[6] we see hemodynamic stability after etomidate induction. Anesthesiologists' enthusiasm for etomidate was tempered, however, by reports that the drug can cause temporary inhibition of steroid synthesis after single doses and infusions.[7] This effect, combined with other minor disadvantages such as myoclonus led to several editorials questioning the role of etomidate in modern anesthetic practice.[8] Because minor adrenocortical suppressive effects were shown to follow even single bolus doses, concerns about the use of etomidate for anesthetic induction arose.[9,10] Etomidate administration was associated with a trend toward a relative increase in mortality.[11]

Etomidate is an intravenous induction anesthetic agent with remarkable cardiovascular stability. It also has sedative-hypnotic properties. Some reports in the literature suggest etomidate can induce adrenal-cortical suppression after single-dose or long-term use,[5,12] whereas others suggest that this inhibition is reversible in normal healthy subjects.[1] In comparative studies with other anesthetic drugs, etomidate is usually described as the drug with the least effect on hemodynamic variables.[13]

Etomidate induction of anesthesia suppresses the usual large increases in plasma cortisol levels associated with anesthesia and surgery.[5,14,15] These levels remain low till at least 4 hours after the onset of anesthesia.[5,14] Etomidate usage for a prolonged duration directly affects adrenal function and inhibits cortisol synthesis.[12,16] Consensus is lacking about the adrenocortical function suppression after a bolus dose of etomidate in adults in various studies.

Fragen et al.,[17] on the other hand, found that etomidate induction depressed the blood cortisol compared to induction with thiopentone.

It was shown by Wagner and White[5] that etomidate inhibited the adrenocortical function for at least 4 hours after its administration for anesthesia induction in adults undergoing cardiac and vascular surgery.

On investigating the effects of etomidate induction, on the neonate after caesarian delivery, it was concluded that etomidate did cause a transient suppression of plasma cortisol concentrations in neonates.[18]

Morel et al. studied the consequences of a single bolus dose of etomidate on adult patients undergoing elective cardiac surgery and concluded that etomidate blunts the hypothalamic-pituitary-adrenal axis response for >24 hours, but it was not associated with increased vasopressor requirements.[19]

Pandey et al. conducted studies investigating the effects of etomidate on plasma cortisol concentrations in pediatric patients with a diagnosis of tetralogy of Fallot undergoing intracardiac repair on CPB. Plasma cortisol values in the etomidate group were low at the end of the operation, and 24 hours postoperatively. Hence, they concluded that etomidate can be used as an anesthetic induction agent to decrease the rise in plasma cortisol levels associated with the intracardiac repair of tetralogy of Fallot in children using cardiopulmonary bypass.[20]

Fragen et al. studied "Effects of etomidate on hormonal responses to surgical stress" and found that Adrenal suppression was preset for 6–8 hours in patients following a single induction dose of etomidate[9,17] and beyond 24 hours following etomidate infusion.[21]

Mornet et al.'s study tell that during etomidate infusion, plasma levels of cortisol, cortisone, and aldosterone drop, while those of 11-deoxycorticosterone, 11-deoxycortisol, progesterone, and 17-hydroxyprogesterone become elevated. Indicating that etomidate inhibits adrenal steroid synthesis primarily by blocking the activity of CYP11B1, also known as 11β-hydroxylase or P450c11. This mitochondrial cytochrome enzyme converts 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone and is 95% homologous to the CYP11B2 (aldolase) enzyme in the pathway leading to aldosterone.[22]

Diago et al. studied "Anti-adrenal action of a subanesthetic dose of etomidate". This helped us to understand the basic mechanism behind the cortisol suppression by etomidate and tells us that the intravenous anesthetic etomidate is known to inhibit cortisol and aldosterone responses to ACTH. A single dose of etomidate was given for induction of anesthesia (0.3 mg/kg) blocked transiently the adrenal mitochondrial cytochrome P450-dependent enzyme 11 hydroxylase, a key enzyme in the synthesis of cortisol and aldosterone. *In vitro* studies have shown that between 5 and 100 nmol/L etomidate produced a marked rise in 11 de-oxycortisol, which indicated an 11 hydroxylase-block.[23]

Mohammad et al. researched "The incidence of relative adrenal insufficiency in patients with septic shock after the administration of etomidate". They found adrenal insufficiency after Etomidate and opined that it is a major risk factor for the development of the shock.[24]

Nooraei et al. studied the "Effects of Vitamin C on Serum Cortisol after Etomidate Induction of Anesthesia". In this study, vitamin C was introduced as a treatment option to decrease etomidate-induced adrenal insufficiency but its actual effect is still controversial.

Temporary adrenocortical suppression, as measured by a reduced response to ACTH stimulation, was documented for 6 hours postoperatively and returned to normal by 20 hours postoperative. They concluded that etomidate could significantly decrease postoperative serum-free cortisol and induce adrenocortical suppression and CRP increase. This effect could be reversed by using vitamin C premedication to maintain serum cortisol at the preoperative level. This would be of paramount importance in fragile patients and high-stress surgeries.[25]

One of the causes of adrenal insufficiency is impaired steroidogenesis due to inhibition of 11β-hydroxylase by the etomidate, which helps in the production of cortisol.

One of the surgical treatments of choice in recent days for symptomatic cholelithiasis is laparoscopic cholecystectomy. Karayiannakis et al. performed a randomized trial on "Systemic stress response after laparoscopic or open cholecystectomy", where they concluded that surgical injury induces a systemic endocrine-metabolic response. It results in stimulation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system.[26]

Stimulation of the adrenal cortex by ACTH results in cortisol secretion which increases rapidly following the start of surgery. Due to a feedback mechanism, circulating cortisol inhibits further secretion of ACTH. The feedback mechanism appears to be lacking after surgery which results in higher concentrations of both the hormones.

As there are a lot of controversies regarding the suppression of cortisol levels after administration of etomidate in patients under surgical stress. This knowledge gap is serving the purpose of the project which will allow to seek answers and give a new insight into the problem. The purpose of the present study was to determine the effects of etomidate on cortisol levels in patients under surgical stress. Serum cortisol levels were measured to see the suppression of the stress response. The study was conducted on patients undergoing laparoscopic cholecystectomy of both genders but excluding those with any comorbid conditions.

## Aim and Objective

The primary objective of the study is to determine the effect of a bolus dose of etomidate on the serum cortisol levels in patients undergoing laparoscopic cholecystectomy, before, and after etomidate administration.

## Materials and Methods

After the Institutional Ethical Committee (IEC) approval and Informed consent, 31 patients were selected based on the American Society Of Anaesthesiologists (ASA) physical status I and II, aged between 20 years and 50 years undergoing laparoscopic cholecystectomy. This prospective, interventional study was done by the Department of Pharmacology in collaboration with the Department of Anesthesia in a tertiary care Medical College and Hospital, Bengaluru

### Inclusion Criteria

- Patients aged between 20 years and 50 years.
- Both genders.
- Confirmed case of cholecystectomy undergoing laparoscopy.
- Patients who consent to participate.

### Exclusion Criteria

- Pregnant women, smokers, alcoholics.
- Diabetes, hypertension.
- Severe systemic disorders like chronic kidney disease, chronic liver disease.

The following data were collected in specially designed CRF:

- Demographic data.
- Disease data.
- Treatment data.
- Preanesthetic medication.
- Investigations.

Thirty-one patients of ASA physical status I and II were enrolled for the study (Flowchart 1) after obtaining their consent and three blood samples were collected. Pre-anesthetic medication consisted of the tab. diazepam 5 mg the previous night and tab. ranitidine 150 mg the previous night and the next day morning at 5 am with sips of water. The patients were induced with 0.4 mg/kg of etomidate intravenously after which, a skeletal muscle relaxant vancuronium of 0.1 mg/kg was administered. Intubation was done after laryngoscopy with an appropriate endotracheal tube. Anesthetic maintenance included administration of nitrous oxide and Isoflurane with oxygen. After surgery, the patients were reversed using neostigmine and glycopyrrolate. Patients were extubated when awake and shifted to the recovery room. After adequate recovery, the patients were shifted to the postoperative ward.

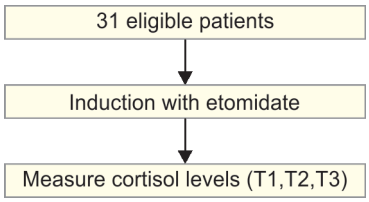
Three venous samples, 2 mL each were drawn from each patient. The first blood sample T1 was drawn at 9 am on the day of the surgery before the induction of etomidate, the second blood sample T2 was 1 hour after the induction of etomidate which coincided with pneumoperitoneum, and the third blood sample T3 was drawn at 9 am the following morning. After the blood samples were collected in the red top vacutainers, they were allowed to clot naturally for about 30 minutes at room temperature after which tubes were centrifuged for 15 minutes at 1,000, 2,000, and 3,000 rpm, respectively, for the first, second, and third samples. After the separation of the serum, they were stored at −80°C until analysis.

Sample analysis for cortisol estimation was done using [Cobas E411]–electrochemiluminescence method.

## Statistical Analysis

Suitable descriptive statistical data were applied to analyze the demographic data, Chi-square test for categorical variables. Appropriate statistical associations were analyzed using RM-ANOVA and Student's *t*-test. Significance was set at $p < 0.05$.

**Flowchart 1:** Etomidate in laparoscopic cholecystectomy



## Observations and Results

In this study, 31 patients were enrolled after satisfying the inclusion and exclusion criteria. All 31 patients were able to complete the study. Table 1 gives the frequency distribution of patients according to gender.

About 58% of the patients under study are Males (M). The remaining 42% are Females (F) (Fig. 1).

Table 2 shows the mean values of cortisol levels of patients in three different time periods.

The above table shows that males showed mean cortisol values of 11.48 ± 2.05 at time T1 which was at baseline, 9.78 ± 1.72 at time T2 which was at pneumoperitoneum, and 5.038 ± 4.22 at time T3 which was at 24 hours. The female patients showed mean cortisol values of 13.407 ± 2.33 at T1, 11.47 ± 2.65 at T2, and 7.065 ± 5.41 at T3. The combined mean cortisol levels of the patients were: 12.291 ± 1.57, 10.49 ± 1.52, and 6.085 ± 3.36 at intervals of T1, T2, and T3, respectively (Tables 2 and 3).

This analysis of the cortisol levels shows that the *p* value (0.11) between T1 vs T2 does not show any significance. The *p* value (0.001) of T1 vs T3 is extremely significant and shows cortisol suppression and helps in proving the objective of the study. The *p* value (0.02) of T2 vs T3 shows the significance and shows the cortisol levels are suppressed.

Since the sample size is 31 we carry out *Z*-test to test whether there is a significant difference in the cortisol levels at different time points namely T1, T2, and T3.

### Null Hypothesis 1

There is no significant difference between cortisol level at time T1 and T2.

**Table 1:** Frequency distribution of patients according to gender

| *Gender* | *No. of patients* | *Percentage* |
|---|---|---|
| Female | 13 | 41.93548387 |
| Male | 18 | 58.06451613 |

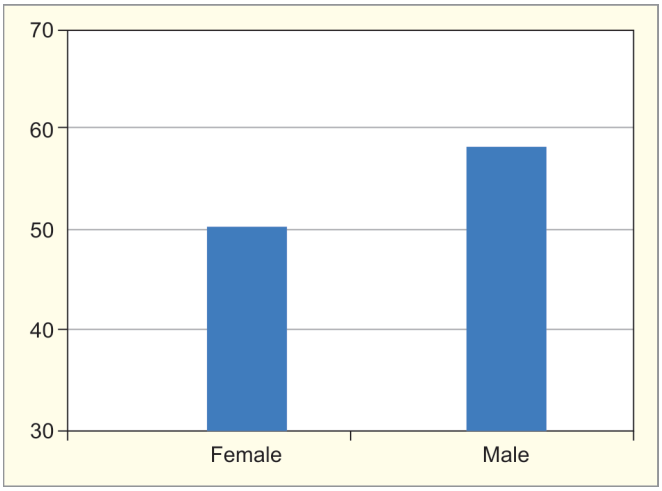



**Fig. 1:** Distribution of males and females in percentage

The calculated value of the *Z*-test is 1.60. At 0.05 level of significance *z*-value is 1.96, therefore we accept the null hypothesis 1 that there is no significant difference between cortisol level at time T1 and T2.

### Null Hypothesis 2

There is no significant difference between cortisol level at time T2 and T3.

The calculated value of the *Z*-test is 2.33. At 0.05 level of significance *Z*-value is 1.96, therefore we reject the null hypothesis 2 that is, we conclude there is a significant difference between cortisol level at time T2 and T3.

But we can accept the null hypothesis 2 at a 0.01 level of significance.

### Null Hypothesis 3

There is no significant difference between cortisol level at time T1 and T3.

The calculated value of the *Z*-test is 3.26. At 0.05 level of significance *Z*-value is 1.96, therefore we reject the Null Hypothesis 3, that is we conclude there is a significant difference between cortisol level at time T2 and T3.

## Discussion

Etomidate, a short-acting intravenous anesthetic agent used for induction of general anesthesia was developed in 1964 and introduced in the market in 1972 in Europe and 1983 in the United States.

Studies on clinical outcome after etomidate in large groups of patients is also lacking.

Consensus is also lacking about the adrenocortical function suppression after a bolus dose of etomidate in adults in various studies, which is why this study becomes important.

The results of this study show that the serum cortisol levels were suppressed in patients under surgical stress who were induced with etomidate, 1 hour after induction (T2), and in some patients up to 24 hours (T3). While in other patients, the cortisol levels returned to normal by 24 hours.

The Student's *t*-test showed significance between T1 vs T3 and T2 vs T3, hence proving the study.

| *Groups* | *T1 vs T2* | *T1 vs T3* | *T2 vs T3* |
|---|---|---|---|
| *p* value | 0.11 | 0.001** | 0.02* |

Paired Student's *t*-test was used for analysis
*$p < 0.05$, **$p < 0.01$

**Table 3:** Analysis using student's *t*-test

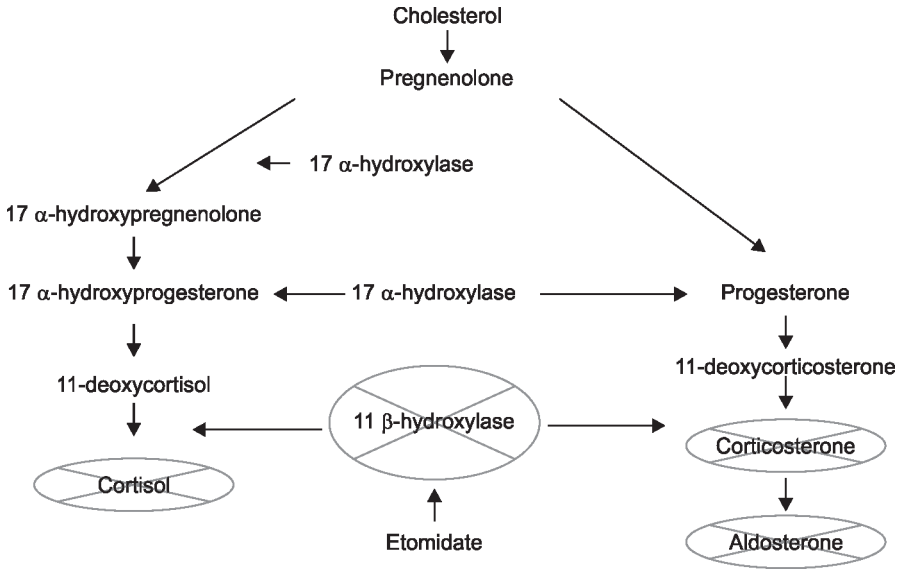
| *Groups* | *T1 vs T2* | *T1 vs T3* | *T2 vs T3* |
|---|---|---|---|
| *p* value | 0.11 | 0.001** | 0.02* |

Paired Student's *t*-test was used for analysis
*$p < 0.05$, **$p < 0.01$

**Table 2:** Mean values of cortisol levels of patients in three different time periods

| *Gender* | *T1 (Baseline)* | *T2 (Pneumoperitoneum)* | *T3 (24 hours)* |
|---|---|---|---|
| Male | 11.486 ± 2.054746 | 9.78088 ± 1.728328 | 5.03887 ± 4.229249 |
| Female | 13.40702 ± 2.33744 | 11.47216923 ± 2.653644 | 7.065485 ± 5.41646 |
| Combined | 12.2916 ± 1.5797 | 10.49013 ± 1.5270 | 6.0850 ± 3.3699 |

**Flowchart 2:** Cortisol synthesis and mechanism of adrenal suppression




Some reports have confirmed an association between administration of etomidate and decreased plasma cortisol levels.[4,9]

Increased plasma levels of hormones of the pituitaryadrenal axis are the typical endocrinologic response to trauma and stress. The suppression of the cortisol levels we observed in patients receiving etomidate is in agreement with the results of all previous studies, except that of Wagner and White[5] who were unable to detect any temporal cortisol changes in a study of very short duration in patients with very minor surgical trauma.

Etomidate inhibits adrenal mitochondrial 11-β hydroxylase, the enzyme responsible for the final conversion of 11-deoxycortisol to cortisol as shown in Flowchart 2. This mechanism is responsible for causing adrenal suppression.

Etomidate induction of anesthesia suppresses the usual large increases in plasma cortisol levels associated with anesthesia and surgery.[5,14,15] These levels remain low till at least 4 hours after the onset of anesthesia.[5,14]

Etomidate was found to suppress normal cortisol and aldosterone increases following surgery as well as adrenal responses to corticotrophin. Adrenal suppression was found to last 6–8 hours in patients following a single induction dose of etomidate.[9,17] Etomidate usage for a prolonged duration directly affects adrenal function and inhibits cortisol synthesis.[12,16] Its suppression lasts for >24 hours following etomidate infusion.[17]

## Conclusion

This study was conducted to assess the effect on cortisol levels by a bolus dose of etomidate in patients undergoing laparoscopic cholecystectomy. Induction of anesthesia with etomidate could significantly decrease postoperative serum-free cortisol and induce adrenocortical suppression. In our study, we did not encounter any complications due to induced adrenocortical suppression. This adrenocortical suppression would be of paramount importance in fragile patients and high-stress surgeries.

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